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Review Article

Pulmonary Hypertension Management Challenges in Pediatric Age Group

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Abstract

The major causes of pulmonary hypertension (PH) in children are congenital heart defect (CHD) and PH associated with prematurity, respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). Idiopathic pulmonary arterial hypertension (PAH) and PAH associated with genetic mutations are also known to manifest in the pediatric age group. This review will mainly discuss the problems encountered in the management of PAH associated with CHD, especially left to right shunts, and in PH associated with premature birth and BPD.

Keywords

- Bronchopulmonary dysplasia
- Congenital heart defect
- Prematurity
- Pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is a rare, but a progressive disease with a high morbidity and mortality rate that affects all age groups. A number of diseases such as cardiopulmonary, autoimmune and infectious diseases, hematological disorders, chromosomal abnormalities, and a number of syndromes and genetic mutations are associated with PH. Based on clinical diagnosis, PH has been classified into 5 major groups; that was updated in 2013 [1]. Gr. 1 known as pulmonary arterial hypertension (PAH) that includes idiopathic (IPAH), heritable (HPAH), and PAH associated with CHD, autoimmune diseases, infection and genetic mutations. Pulmonary capillary hemangioma and pulmonary venous obstructive disease are included in Gr.1 as subcategory 1' and persistent pulmonary hypertension of the newborn (PPHN) as 1". Gr. 2 includes PH associated with congenital and acquired left heart diseases; Gr. 3 comprises congenital and acquired lung diseases; Gr. 4 includes PH associated with chronic thromboembolic disease. A miscellaneous group of diseases such as hematological disorders, metabolic diseases etc are included in Gr. 5. Pathobiology of PAH is quite complex involving a number of signaling pathways [2]. Irrespective of the underlying disease, endothelial disruption/dysfunction is a key underlying feature of PH. It leads to impaired vascular reactivity, medial hypertrophy, elevated pulmonary artery pressure (PAP), right ventricular hypertrophy; with subsequent development of neointima and plexiform lesions, RV failure and premature death.

Endothelial cells (EC) regulate vascular reactivity, coagulation and barrier function, thus, maintain vascular homeostasis. Caveolin-1 is the major protein constituent of caveolae; specialized micro-domains found on plasmalemmal membranes of a number of cells such as endothelial cells (EC), epithelial cells, smooth muscle cells (SMC), fibroblasts, adipocytes and

others. Caveolin-1 interacts with a numerous signaling molecules that reside in or recruited to caveolae, and keeps most of these molecules in an inhibitory conformation. A large number of signaling pathways that are implicated in PH interact with endothelial caveolin-1. Disruption or dysfunction of endothelial caveolin-1 induced by injury such as inflammation, drug toxicity, increased shear stress and hypoxia acts as the initiating factor in the pathogenesis of PH and also contributes to the progression of the disease [3]. Experimental studies with monocrotaline (MCT) model of PH have revealed progressive disruption of EC, loss of endothelial caveolin-1, reciprocal activation of proliferative pathways, and significant molecular and pathological changes in the pulmonary vasculature before the onset of PH [4]. The rescue of caveolin-1 prevents PH; however, once the PH is established, the rescue of endothelial caveolin-1 or the attenuation of PH does not seem likely [5]. Extensive disruption of EC coupled with the loss of endothelial caveolin-1 is associated with enhanced expression of caveolin-1 in SMC. Isolated pulmonary arterial SMC from IPAH patients exhibit enhanced caveolin-1 expression, increased capacitative Ca^{2+} entry and DNA synthesis. Silencing caveolin-1 inhibits both capacitative Ca^{2+} entry and DNA synthesis [6], indicating that this caveolin-1 becomes pro-proliferative. Thus, it is possible that this enhanced expression of caveolin-1 is partly responsible for SMC phenotype change from contractile to synthetic. Recent studies have shown that exposing the MCT-treated rats to hypoxia accelerates the disease process. These rats not only show extensive loss of endothelial caveolin-1 and enhanced expression of caveolin-1 in SMC but also neointima formation [7]. Furthermore, enhanced expression of caveolin-1 in SMC has been shown in PAH associated with CHD, drug toxicity, IPAH, HPAH and in BPD-associated PH [6-9]. Importantly, enhanced caveolin-1 expression in SMC is observed only in the arteries that exhibit extensive endothelial caveolin-1 loss accompanied by significant EC damage and loss. It is

possible that the loss of EC results in SMC being exposed to direct pressure and shear stress which in part may be responsible for translocation of caveolin-1 to non-caveolar sites on the plasma membrane. This view is supported by *in-vitro* studies showing cyclic stretch-induced translocation of caveolin-1 from caveolae to non-caveolar sites where it participates in cell proliferation. Furthermore, caveolin-1^{-/-} SMC do not proliferate on exposure to cyclic stretch [10-12]. Interestingly, hypoxia results in a tight caveolin-1 and endothelial nitric oxide synthase (eNOS) complex formation, rendering both molecules dysfunctional; but it does not cause a physical disruption of EC or the loss of endothelial caveolin-1. The SMC are not exposed to direct pressure or shear stress; with the result, this state is not accompanied by an enhanced expression of caveolin-1 in SMC [13,14]. This may be the reason why hypoxia-induced PH is reversible on removal from hypoxia or by treating with statins to disrupt cholesterol resulting in the dissociation of caveolin-1 from eNOS. Loss of endothelial caveolin-1 coupled with enhanced caveolin-1 expression in SMC has been observed in infants with PAH-CHD; and also in BPD with PH. We have further shown that the elevated PAP accompanied by inflammation or increased pulmonary blood flow leads to the disruption/loss of EC and loss of endothelial caveolin-1 followed by enhanced expression of caveolin-1 in SMC. The elevated PAP alone does not disrupt EC, and is not associated with endothelial caveolin-1 loss or enhanced expression of caveolin-1 in SMC [8]. These observations suggest the progression of PH may depend on the extent and the type of EC damage and its repair capabilities.

In children, the major causes of PH are CHD, PPHN, and PH associated with lung diseases such as RDS, BPD, and congenital defects associated with hypoplasia of the lungs [15,16]. Medial hypertrophy is the main feature of PH in the pediatric age group. With increasing age, other pathological features such as intimal proliferation, concentric fibrosis and subsequently dilatation and plexiform lesions begin to appear [17]. More than 80% of pediatric patients have transient PH. These include resolution of PPHN, and the majority of CHD cases that become free of PH after the surgical correction of the defect [18]. Poor outcome has been reported in children with IPAH and HPAH associated with BMPRII mutation [19].

BPD is a major cause of neonatal morbidity and mortality. Antenatal and perinatal problems have adverse effects on vascular and alveolar development. Preterm delivery disrupts normal pulmonary vascular and broncho-alveolar development which leads to reduced cross sectional area of the pulmonary vasculature resulting in increased pulmonary vascular resistance (PVR) and PH [20]. Furthermore, preterm birth has been reported to have an increased risk of developing PH in children and adults even after adjusting for known risk factors such as chromosomal abnormalities, CHD, chronic lung disease, congenital diaphragmatic hernia [21].

Congenital heart defect & pulmonary hypertension

CHD occurs in 8-10/1000 live births. PAH is the major complication of CHD associated with left to right shunts, and complex anomalies such as transposition of great vessels, truncus arteriosus and single ventricle pathophysiology. In children, about 50% of cases of PAH have underlying CHD [22,23]. In the recent PH classification, PAH-CHD has been further classified as:

1. Eisenmenger syndrome, 2. PAH and systemic to pulmonary shunt, 3. PAH coincidental with CHD, and 4. Post-operative PAH [1]. Importantly, the prognosis in the PAH-CHD subgroups comprising small defects and surgically corrected defects is worse compared to Eisenmenger syndrome [24]. In a Dutch series, the prevalence of PAH associated with CHD was reported to be 42%, with septal defect 6.1% and 3% in previously closed shunts [25]. Review of patients registered in the UK Pulmonary Hypertension Service (years 2001-2006) revealed the survival rate in the "associated" PAH to be 92.3%, 83.8% and 56.9% at 1, 3 and 5 yrs. In this study also, the worse prognosis was observed in post-operative PAH-CHD [23]. In another study that included 1013 patients (1977-1990) with atrial septal defect (ASD) 2°, ASD1° and ventricular septal defect (VSD) who underwent surgical correction (mean age 8.5 years); the incidence of PAH was reported to be 2.1% immediately after the surgical closure of the defect, and >15% 50 years following the closure [26].

The probability of developing PAH in left to right shunt at pre-tricuspid level such as ASD is rare. However, PAH in post-tricuspid lesions such as VSD and patent ductus arteriosus (PDA) can occur during the first year; and if the defects are left untreated, it is likely that 50% of patients will develop Eisenmenger disease [27]. Impaired growth of pulmonary vasculature has been reported in CHD with increased pulmonary blood flow leading to PAH [28]. Furthermore, increased PAP a day after surgical correction of the defect correlated well with histological changes in the lungs. Despite significant histological changes (Heath Edward Classification, grade II and III) observed before surgery, a year later, only 2 out of 33 infants operated on before the age of 9 months had increased PAP, but normal PVR. However, infants operated after the age of 2 years who had significant pulmonary vascular changes (Heath Edward grade III) exhibited increased PAP and PVR [29]. Early surgical closure of the defect preferably before the age of one year is likely to prevent the development of Eisenmenger syndrome in the majority of cases.

A few cases of children with small VSD or spontaneously closed VSD have been reported to have developed PAH. An infant at the age of 4 weeks was diagnosed to have VSD and heart failure. He was started on digoxin and lasix. At 2 months, cardiac catheterization revealed a large left to right shunt (Qp/Qs 3.7:1) and PAP (60/20, m32 mmHg). He continued to improve, and at 16 months, a repeat cardiac catheterization revealed a small VSD (PAP 38/16 m20 mmHg, Qp/Qs, 1.5:1). Around 4 years of age, he was found to have spontaneous closure of VSD associated with PAH (PAP 90/70 m79 mmHg) which was somewhat responsive to oxygen (PAP on oxygen 72/50 m59 mmHg) [30]. There is another report of a 4 year child with a VSD. At 6 years, cardiac catheterization revealed PAP 38/14 m24 mmHg and a Qp/Qs ratio of 1.9:1. At 11 years of age, the murmur remained unchanged; cardiac catheterization revealed an elevation of PAP (42/22 m28 mmHg) and a smaller shunt (Qp/Qs 1.2:1). At 16 years the, PAP had increased to 86/47 m60 mmHg, and left to right shunt (Qp/Qs, 1.4:1); and he underwent surgical closure of the defect. Two years later he still had elevated PAP (PAP 60/29, m48 mmHg) but no shunt [31]. Another child (age 8 months) was diagnosed to have a moderate VSD with left to right shunt. There was a history of feeding difficulty, otitis media and cyanosis on crying since the age of a month. She was lost to follow-up and

presented at the age of 4 years and 3 months with a history of syncope, agitation, and anxiety. She died at the age of 4.5 years during a syncopal attack. At autopsy, the right heart was found to be hypertrophied, VSD appeared closed, pulmonary vasculature was abnormal exhibiting medial thickening and neointimal lesions [32].

We had an opportunity to examine vascular reactivity in pulmonary micro-vessels from 2 infants; identical age (13 mos), both with Down syndrome, atrioventricular canal defect, PAH (similar pulmonary artery pressure), heart failure and similar lung histology (Heath Edward classification grade II). Normal endothelium-dependent relaxation response was observed in the pulmonary micro-vessel from one infant; during surgery, after the closure of the defect the pulmonary artery pressure returned to normal, and the infant had a smooth post-operative course. The micro-vessel from the second infant exhibited attenuated endothelium-dependent relaxation response. Not surprisingly, the pulmonary artery pressure did not drop after surgical closure of the defect. The infant had a stormy post-operative course [15]. Another infant with Down syndrome had atrioventricular canal defect repaired elsewhere at the age of 4 months. At the age of about 12 months he was diagnosed to have asthma and was hospitalized locally twice during the following year for severe asthma. At the age of 23 months he was admitted to our pediatric intensive care unit with respiratory syncytial viral infection. Echocardiogram revealed significant PAH (estimated right ventricular systolic pressure 79 mmHg), and eventually he succumbed. His cardiac follow up history was not known, but he was not on any cardiac medication. His lung section revealed significant disruption of EC in pulmonary arteries, loss of endothelial caveolin-1 and enhanced expression of caveolin-1 in SMC indicative of significant vascular pathology [8]. Another infant, soon after birth was found to have VSD, PDA and heart failure. He was treated with anti-failure medications (digoxin and lasix). His heart failure seemed to have improved. However, at 10 months of age, his oxygen saturation dropped to 93%; he underwent cardiac catheterization and was found to have a patent foramen ovale, a small PDA and a mean PAP, 46 mmHg. Because of the unusual presentation, a lung biopsy was obtained, which revealed medial hypertrophy, some arteries exhibited loss of endothelial caveolin-1 and enhanced expression of caveolin-1 in SMC [8]. He is doing well on sildenafil.

Summary

Infants and children with small VSD or surgically closed shunt defect have been shown to develop PAH during late childhood and adulthood. The studies cited above show that endothelial damage and loss can occur early during infancy. The EC damage observed in infants with shunt defects may progress insidiously, even after the closure of the defect leading to PAH. Clinically, one cannot assess the underlying endothelial damage. There are no biomarkers to identify EC damage before the onset of PH. It is significant, that even after the spontaneous closure of VSD or early surgical closure of the defect, the EC damage occurred during the early phase of the disease may continue to progress. The important question is whether these patients have defective endothelial progenitor cells and/or defect in the repair mechanism. If the pulmonary artery pressure does not drop to

normal levels immediately after the surgical closure of the defect, irrespective of the age, the patients need to be carefully followed. Failure of normalization of PAP after the surgical closure of the defect is indicative of EC dysfunction/disruption. Treatment with PH medication/s may facilitate the recovery of the endothelial cells, and the normalization of the pulmonary flow may allow endothelial recovery. Based on the reports cited above, patients with small VSD, and successfully closed VSD and atrio-ventricular canal defect need to be followed through the late childhood and adulthood. If these patients exhibit respiratory symptoms, the possibility of underlying PAH needs to be considered.

Children with ASD2° are not likely to develop PAH, because in ASD2° increased pulmonary flow is associated with low pressure that does not lead to EC damage, unless the shunt is left uncorrected for several years. Most cases of the PAH associated with ASD2° are seen during early to late adulthood.

Premature Birth, BPD & pulmonary hypertension

BPD is defined as a need for supplemental O₂ at 36 post-menstrual age [33]. BPD was originally described by Northway et al. [34], as chronic lung disease in newborn infants with RDS treated with positive-pressure ventilation and O₂. With the improved management such as antenatal steroid therapy, administration of surfactant and non-invasive ventilation strategies has improved the survival of extremely preterm infants. The major problem with these infants is the arrested lung (alveolar and vascular) growth which puts them at a risk of developing BPD. Antenatal exposure to proinflammatory cytokines has been thought to cause lung injury and predispose premature infants to the development of BPD. BPD in these infants is different from the "classical" BPD. The important features are arrested pulmonary vascular and alveolar growth resulting in pulmonary vascular hypoplasia and alveolar simplification. BPD affects about 33-46% of extremely low birth weight infants, and depending on the severity of BPD, PH complicates 17-37% of infants [35-37]. In an experimental model of BPD, prenatal inflammation followed by neonatal oxidant stress is reported to lead to poor alveolarization and diffused interstitial fibrosis [38]. Importantly, resuscitation of preterm neonates with 30% oxygen results in less oxidative stress, inflammation, need for oxygen, and diminishes the risk of BPD. It is likely that high O₂ used during resuscitation in the delivery room may contribute to chronic lung disease [39]. In a series of 145 extremely low birth weight infants, the incidence of PH was found to be 17.9%; and infants with PH were more likely to have had received oxygen on day 28 compared with the ones without PH [40]. The presence of PH detected early, i.e. within 14 days in very low birth weight infants is associated with moderate to severe BPD and increased mortality rate [41,42]. Furthermore, the survival rate of infants with PH complicating BPD is as low as 53% at 2 years of age [43].

Vascular changes, angiogenesis and BPD

In a rodent model of BPD, recently it was shown impaired endothelium-dependent relaxation to acetylcholine in pulmonary arteries, but normal response to NO donor, nitroprusside, decreased eNOS phosphorylation at Ser1177 activating site; and increased contractile response to serotonin and phenylephrine. In addition, cytosolic Ca²⁺ levels were increased in the pulmonary

artery SMC indicating both EC and SMC dysfunction in BPD [44]. In fetal baboon studies, epithelial cells appeared to express all 3 forms of NOS. During the third trimester, the NOS expression is upregulated. In premature baboons, a significant reduction in eNOS and nNOS was accompanied by chronic lung disease; these animals were given surfactant and ventilated to maintain PaO₂ levels between 55-70 Torr. Treatment with inhaled nitric oxide (iNO, 5 parts/million) at 1 hr of birth, continued for 14 days exhibited increased terminal bronchiolar proliferation, less deposition of elastin in the parenchyma, reduced tropoelastin mRNA and decreased PAP [45]. Deficiency of eNOS in mice causes major defects in lung morphogenesis leading to respiratory distress and death within few hours of birth. A higher prevalence of BPD has been reported in infants with eNOS polymorphisms (TC+CCrs2070744eNOS and GT-TTrs1799983eNOS) [46]. Lungs in mutant mice exhibit increased thickening of alveolar septae and reduced surfactant. In the wild type mice, there is progressive increase in mRNA levels for VEGF-A, angiopoietin-1, and their receptors Flk-1 and Tie2; whereas these were significantly reduced in eNOS^{-/-} mice and the surfactant in these mice was defective [47]. Even mild hypoxia has been shown to impair angiogenesis and alveolar development [48].

In a small number of ventilated premature infants (gestational age 24-27 weeks) with BPD, significant reduction in the growth factors involved in the development of microvasculature such as VEGFB, VEGFR2 (KDR/Flk-1) and Tie2 was present compared with the non-ventilated infants of the same age. Genes involved in the extracellular matrix remodeling such as thrombospondin-1, collagen XVIII alpha-1 and tissue inhibitor of metalloproteinase-1 were up regulated. In addition, increased mRNA levels of cytokines and chemokines were observed in short-term ventilated lungs [49]. Bhatt et al. [50], have shown reduced expression of PECAM-1 (protein and mRNA) and VEGF mRNA, and poor expression of Flt-1 and Tie2 in pulmonary vasculature. Furthermore, absence of PECAM-1 has been reported to impair alveolarization in a murine model [51]. Lung biopsy section from an infant with BPD-PH revealed significant reduction in the expression of caveolin-1 in EC, thickened media without enhanced expression of caveolin-1 in SMC. Another infant with BPD-PH revealed extensive damage/loss of EC accompanied by enhanced expression of caveolin-1 in SMC similar to what has been observed in patients with IPAH, HPAH and PAH associated with CHD. It is likely that inflammation in BPD damages EC which may become progressive and affect the prognosis negatively. In contrast, the pulmonary arteries from infants with RDS revealed thickened media without enhanced expression of caveolin-1 in SMC and intact EC without any loss of caveolin-1 despite elevated PAP [7-9]. It is possible that similar to what is observed in the hypoxia model of PH, caveolin-1 and eNOS form a tight complex in EC, thus rendering both molecules dysfunctional in RDS. Treatment with antiangiogenic factors in a rodent model has been shown to significantly reduce alveolarization; whereas treatment with rhVEGF injection (intramuscular) or intra-tracheal adenovirus-mediated VEGF gene therapy improved alveolarization [52-54].

Kim et al. [55], have reported increased ratio of endostatin (anti-angiogenic) to angiopoietin-1 (proangiogenic) at 7days in premature infants with severe BPD and PH. Endostatin is known to antagonize VEGFA, and disrupt angiogenesis. Extracellular

superoxide dismutase (EC SOD) over expression attenuates oxidative stress-induced inhibition of angiogenesis. EC SOD transgenic mice when exposed to hyperoxia were protected from reactive oxygen species (ROS) production and the expression of endothelial progenitor cells, and VEGF were not affected; however, PECAM-1 levels were reduced both in wild type and transgenic mice [56]. The levels of antioxidants increase during gestation. The interruption of placental-fetal transfer of antioxidants coupled with failure of inducing antioxidants during oxidative stress is a serious problem in premature infants. However, clinical trials with endotracheal administration of SOD were not successful in preventing BPD [57].

Management of BPD and PH in premature infants

Antenatal steroids, surfactant administration, improved ventilation and PH management strategies have improved survival in very premature infants. However, the disrupted broncho-alveolar and pulmonary vascular development continues to pose a daunting challenge in the management of these premature infants.

Surfactant: Surfactant is synthesized and secreted by alveolar type II (ATII) cells, starting during the canalicular stage (16-26 weeks gestation), and is assembled into acidic organelles called lamellar bodies. It consists of 70-80% phospholipids, 10% surfactant proteins (SP-A, SP-B, SP-C, and SP-D) 10% lipids, mainly cholesterol. The major component is saturated phosphatidylcholine that forms a stable surface active film in the alveolae to sustain minimal surface tension during expiration. The surfactant-associated proteins, SP-A, SP-B and SP-C interact with surfactant phospholipids to facilitate in reducing surface tension, and prevent the lungs from collapsing. Infants requiring continuous respiratory support after 7 days of age have been shown to experience transient episodes of surfactant dysfunction associated with deficiency of SP-B and SP-C [58-60]. A randomized trial with the use of late surfactant or sham was recently carried out in infants (gestational age 25.2 ± 1.2 weeks, weight 701 ± 16.49 g, n=511) requiring ventilation at 7-14 days and receiving iNO. Surfactant was well tolerated by these infants; however, it did not improve survival without BPD at 36-40 weeks post-menstrual age [61]. Interestingly, in *in-vitro* studies, it has been shown that NO reduces the surfactant gene in ATII cells in a dose dependent manner [62]. Furthermore, oxidant injury has been shown to induce surfactant inactivation [63], and thus, contribute to the development of BPD.

Hyperoxia and mechanical ventilation: A number of premature infants do require ventilatory and O₂ support, both of which can contribute to BPD. Chronic lung disease from prolonged mechanical ventilation inhibits normal postnatal drop in PVR and leads to structural abnormalities such as decreased numbers of micro vessels, increased pulmonary artery SMC thickening and decreased expression of soluble guanylate cyclase (sGC). The ventilated lambs were given iNO at 2 weeks (15 parts/million), PVR dropped by 20%, but iNO had no effect at 3 weeks of ventilation. Infusion of 8-bromoguanylate phosphate reduced PVR, indicating that sGC may be deficient or defective [64]. Furthermore, 3-4 weeks ventilation in preterm lamb resulted in the dysregulation of elastin synthesis and disordered accumulation of elastin in the alveolar wall [65-67]. In mice,

mechanical Ventilation with 40% O₂ resulted in the reduction of genes that regulate lung septation and angiogenesis such as VEGF A, VEGF-R2, PDGF A, tenascin C and an increase in TGF β expression. Interestingly, mechanical ventilation without hyperoxia had similar results; indicating that shear stress itself can disrupt elastin deposition [68, 69]. In a recent study, higher cumulative supplemental oxygen at 14 days in premature infant (gestational age 25.2 ± 1.2 weeks, birth weight 700 ± 165 g) directly correlated with increased incidence of BPD or death [70]. Furthermore, in a murine model, 2 weeks of hyperoxia resulted in alveolar simplification, low vascular density, low sGC activity and increased Phosphodiesterase (PDE) 5 activity [71]. Mechanical ventilation and hyperoxia used to ameliorate hypoxic condition are associated with serious problems in these infants; especially in the presence of low levels of antioxidants.

Inhaled nitric oxide: NO is required for vascular development and it mediates neovascularization via VEGF. Inhaled NO is an effective treatment. However, up to 40% of PPHN are non-responders to iNO. The results of iNO therapy in the premature infants have been contradictory. In premature infants, especially low weight (<1500 g) or gestational age less than 29 weeks do not respond to iNO. Furthermore, iNO does not decrease the death rate or BPD. The response to iNO gets better in infants with increasing gestational age [72,73]. In another study, iNO given to preterm infants weighing <1500 g did not decrease the incidence of BPD or BPD-associated mortality; although it improved short term oxygenation without any side effects [74]. Treatment with iNO has been shown to reduce several inflammatory and fibrotic mediators in tracheal aspirates from preterm infants, but survival without BPD was not affected [75]. Non-invasive iNO although safe was found not to have any effect on the need for mechanical ventilation, BPD or death [76]. In addition, late treatment with surfactant in ventilated infants and iNO was found to be well tolerated but without any improvement in survival without BPD [61]. Randomized control trials (comprising 3298 infants, <37 weeks gestation) showed no statistical differences between the effects of iNO or placebo on death or severe neurologic effects [77]. In another study which analyzed premature infants (26 weeks gestation, weight <1250 g) from 21 centers, who required ventilation support between 7-21 days; 294 infants received iNO and 288 infants were given placebo. In the iNO group, the survival without BPD at 36 weeks post-menstrual age was 43.9% compared to 36.8% in the placebo group. In addition, the iNO group had shorter course of supplemental oxygen and were discharged sooner [78]. VEGF R2 inhibitor (sugen 5416) has been used as a model for BPD in neonatal rat pups. Inhaled NO treatment reduced sugen 5416-induced endothelial cell apoptosis [79]. Hypoxia-inducible factor (Hif)-2 α is expressed in AII cells, and VEGF, a critical factor for lung maturation is its down-stream target. VEGF is thought to convert glycogen to surfactant phospholipids. Hif-2 α ^{-/-} mice dies within 2-3 hours of birth of serious respiratory problems due to lung collapse. Intra-tracheal administration of hVEGF improved alveolar function [80]. Furthermore, adult rats exposed to >95% O₂ exhibit significant reduction in the levels of VEGF mRNA and protein within 48 hours [81].

NO increases NO-sGC-cGMP pathway, but NO in combination with O₂ produces peroxynitrite, a potent oxidant. During oxidative

stress, heme-bound sGC gets oxidized resulting in its inactivation and degradation. Soluble GC plays a role in protecting the lungs from injury and improves alveolarization [82,83]. Furthermore, sGC activators blunt hyperoxia-induced Ca²⁺ responses in developing human airway smooth muscle [84]. Interestingly, in a lamb PPHN model, cinaciguat, a sGC activator induced significantly increased pulmonary vasodilatation compared with 100% O₂, acetylcholine or iNO [85]. These studies indicate that sGC activator may be an ideal choice when iNO is ineffective or it participates in oxidative stress.

Sildenafil: Sildenafil is a PDE5 blocker that prevents cGMP degradation. It is in use for the treatment of PH in adults and children. Sildenafil has been shown to improve alveolar growth in rat pups exposed to hyperoxia [86], and it improves angiogenesis via activating HIF 1/2- α and VEGF [87]. Thirteen infants (>35.5 weeks gestational age) were treated with sildenafil (n=7) and placebo (n=6). The oxygen index improved within 6-30 hours in the sildenafil and 6/7 infants survived whereas only 1/6 in the placebo group survived [88]. König et al. [89], reviewed infants (<28 wks gestation) on mechanical ventilation, who were treated with Sildenafil (7 patients) or placebo (10 patients). In the sildenafil group 3/7 deaths occurred and the duration of inspiratory support was much longer; whereas there was 1/10 death in the placebo group. However, in one study, sildenafil treatment in preterm infants with BPD and PH resulted in significant reduction in pulmonary artery pressure but had no improvement in gas exchange [90]. In another study, that involved 22 infants (mean gestational age 25.6 ± 1.3 wks, weight 613 ± 181 g), 18 infants were treated for symptomatic PDA. Six died before discharge (5 of respiratory failure, 1 of sepsis). Sildenafil treatment was associated with significant echocardiographic improvement in PH and decreased O₂ requirement [91]. Interestingly, it is the sildenafil, and not prostacyclin or bosentan that has angiogenic properties [92].

Bosentan: During the third trimester, fetal pulmonary circulation develops a significant vasoconstrictor response. Endothelin (ET)-1 produced by EC is a potent vasoconstrictor by acting on ETA receptors on SMC; its action on EC via ETB receptors leads to NO generation and vascular relaxation. Bosentan is a dual ETA and ETB blocker and is in use for the treatment of PH in adults and children. Recent randomized trial with bosentan/placebo in infants with PPHN born at >34 weeks gestation showed that bosentan, although well tolerated did not improve oxygenation nor had any clinical benefit [93]. One of the major problems in BPD is the disruption of angiogenesis. ET-1 has been shown to impair angiogenesis through Rho kinase as well as by decreasing the PPAR γ expression. Although ET1 had no effect of the growth of pulmonary artery EC; but the tube formation was reduced [94,95]. In *in-vitro* studies with human umbilical vascular endothelial cells, ET1 has been shown to induce proangiogenic phenotype, increase MMP2 production via ETB receptors, promoting cell migration and neovascularization [96]. Bosentan has been shown to increase sildenafil clearance resulting in decreased plasma concentration [97]. Based on these results, it seems that the use of bosentan in premature infants may not be desirable.

Inhaled Prostacyclin: Lung inflation and stretching of

alveolar epithelial barrier is an important stimulus for surfactant secretion in ATII cells. In the presence of prostacyclin analog, ATII cells exhibit marked increase in stretch-induced surfactant secretion concomitantly with enhanced cAMP accumulation. Addition of PDE type II and IV inhibitors further increased both cAMP and surfactant. Increasing cGMP had no effect on surfactant. NO decreased ATP content and surfactant synthesis in ATII cells within 2 hours [98]. This study indicates that prostanoids have a positive effect on surfactant production. Furthermore, epoprostanol inhalation has been shown to improve oxygen index better in infants compared with children [99].

The premature infants require mechanical ventilation which contributes to the production of BPD. Several case reports have been published showing inhaled prostacyclin to be quite effective in getting the infants off the ventilator sooner. In one study, premature infants (23-25 weeks gestation, n=4) weighing 448-645 g spontaneously breathing (85-100% O₂) had the evidence of hypoxemia and right to left shunt at the PDA level. Importantly, the first inhalation of iloprost was accompanied by improved oxygenation and a decrease in the estimated pulmonary artery pressure. The treatment was continued for 7 days. They all survived and left the hospital on no medication. During the subsequent follow up 2 infants had symptoms of chronic lung disease, and one had grade 1 intracranial hemorrhage [100]. In another study (retrospective) 15 premature babies (gestational age 25-37 weeks) diagnosed to have respiratory distress and PH were treated with inhaled iloprost. They showed significant improvement in oxygen requirement and a reduction in estimated pulmonary artery pressure, and were able to come off the ventilator within a week [101]. A premature infant (28 weeks gestation) treated with surfactant and hyperventilation failed to improve, but with aerosolized prostacyclin, oxygenation improved and the infant was off the ventilator in 108 hrs. Not surprisingly, the intravenous prostacyclin had no effect on oxygenation [102]. Another report of 4 premature infants (26.7-33.7 weeks gestation, 3 with hyaline membrane disease and 1 with septicemia) had hypoxemia and right to left shunt at PDA level. Endo-tracheal instillation of prostacyclin improved oxygenation, oxygen index and reversed the shunt without any systemic effects [103]. In addition, improvement with inhaled prostacyclin was observed in 4 neonates with PPHN and hypoxemia refractory to inhaled nitric oxide. The condition of one infant subsequently deteriorated, and was found to have alveolar capillary dysplasia at autopsy. The surviving infants were discharged with normal oxygen saturation in room air [104]. Bindl et al. [105], described two infants: case 1, born at 35 weeks gestation, birth weight 4.08 kg (maternal obesity and diabetes) required nasal oxygen at 6 hours, and intubation and mechanical ventilation by 20 hours. The infant had PH with right to left shunt at the atrial level. Aerosolized prostacyclin improved oxygenation and the shunt reversed. He was extubated after 40 hrs and his echo had normalized. Case 2: a fetus was found to have hydrothorax at 23 weeks gestation underwent fetal thoracentesis 6 times; and ascites was present at 34 weeks gestation. The infant was born at 37 weeks gestation weighing 360 g; needed intubation 12 minutes after birth because of hypoxemia. At 24 hrs, he was diagnosed to have PH with right to left shunt at the atrial and PDA levels. As soon as aerosolized PGI2

was administered, the oxygenation improved without any effect on PH. At the end of 30 minutes, IV PGI2 was started. Pulmonary pressure returned to normal and was extubated in 16 days. Gokce et al. [106], described 2 very low birth weight infants: case1, a male infant weighing 800g (27 weeks gestation) required intubation and was given surfactant. He was found to have PH with right to left shunt at PDA level. Despite 100% O₂, another dose of surfactant and vasopressors, the infant failed to improve. He was started on inhaled iloprost; within 12 hours O₂ saturation and index improved, the PAP dropped, the shunt at the PDA level reversed. Iloprost was gradually stopped on the 4th day, and on the 5th day echocardiography revealed normal PA pressure. He was weaned off the ventilator. Case 2: a female weighing 920 g (28 weeks gestation) was born by an emergency c-section because of maternal uncontrolled hypertension and premature rupture of the membrane. She had respiratory distress soon after birth. Despite surfactant and conventional therapy, the condition deteriorated. Echocardiogram on the second day revealed PH (estimated systolic pressure 77 mmHg). Inhaled iloprost was started, the O₂ saturation increased and the PAP dropped to 47 mmHg. On the third day, the PAP had returned to normal, and the oxygen Index had normalized. Iloprost was gradually discontinued on the 4th day. She was weaned off the ventilator on the 6th day. These cases illustrate that the inhaled prostacyclin is effective in shortening the course of mechanical ventilation.

SUMMARY

Premature infants born with arrested lung growth that includes alveolar simplification and impaired pulmonary vascular growth are at a greater risk of developing BPD; and the associated PH makes the prognosis worse. Hyperoxia and mechanical ventilation further damage the lungs; and the duration and the concentration of O₂ are risk factors for the development of lung damage. Non-invasive ventilation, when possible, has proven to be a better alternative. The treatment with iNO has not been shown to be beneficial in premature infants; although it may be useful in full term infants with hypoxemia and/or PPHN. Furthermore, iNO in combination with O₂ leads to oxidative stress that can further damage the lungs. Recent experimental studies with sGC activators have produced encouraging results. These activators would produce cGMP bypassing NO, thus avoiding its adverse effects. Currently, these agents are being tried in adult with PH; however, more studies are required before its use in premature infants.

A case could be made for the use of inhaled prostacyclin or its analog in preterm infants requiring mechanical ventilation. 1. Several case reports show that the use of inhaled prostacyclin results in shorter duration of mechanical ventilation and clinical improvement. 2. In *in-vitro* studies, prostacyclin has been shown to increase stretch-induced surfactant production [96], whereas NO and oxidative stress have negative effect on surfactant [62,63]. 3. In experimental models (rodents), high tidal volume ventilation has been shown to increase lung cGMP levels leading to endothelial barrier dysfunction, whereas iloprost attenuates stretch-induced endothelial monolayer disruption [107,108]. Once off the ventilator, these infants could be treated with sildenafil for a period to facilitate angiogenesis. It has been suggested that the exposure of the developing lungs to injury

such as oxidative stress may also contribute to pulmonary vascular disease in later life [109]. Furthermore, preterm birth with or without lung injury has been shown to put patients at a risk of developing PH in later years. These patients need to be followed in order to detect PH early and start therapy in order to halt the progression of the disease and possibly reverse it.

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