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The 13th Bengt Robertson Memorial Lecture: Pulmonary Hypertension: the Hidden Danger for Newborns

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Abstract

Despite growing awareness of the clinical importance of pulmonary hypertension (PH) in preterm infants, uncertainty persists regarding the different clinical settings in which abnormalities of pulmonary vascular growth, function and structure contribute to high morbidity and mortality, and potential interventions to improve outcomes are uncertain. A major gap for improving outcomes of preterm infants with PH has been the limited characterization of the distinct settings of PH and related disease-specific mechanisms in preterm infants that represent diverse pulmonary vascular phenotypes of prematurity. In comparison with term newborns, preterm infants have a higher risk for developing hypoxemia due to supra-systemic levels of PH in preterm infants shortly after birth, or persistent pulmonary hypertension of the newborn (PPHN). Variable and milder levels of PH have also been demonstrated in preterm infants without evidence of severe hypoxemic respiratory failure, suggesting delayed vascular transition of the lung which is associated with higher risks of mortality and developing bronchopulmonary dysplasia (BPD). In addition, early echocardiographic signs of PH at day 7 are strongly associated with the subsequent diagnosis of BPD, late PH and respiratory disease throughout early childhood. In infants with evolving or established BPD, PH that persists beyond the first few months of life in preterm infants is associated with high mortality. Recent data further show that PVD can persist and cause PH in prematurely-born adults. Overall, more precise characterization and studies of diverse pulmonary vascular phenotypes in preterm infants will be likely to improve the development of therapeutic strategies to optimize care of preterm infants with PH.

Keywords

Pulmonary hypertension; neonate; preterm; persistent pulmonary hypertension of the newborn; pulmonary vascular disease; bronchopulmonary dysplasia

Introduction

It is my pleasure to have this opportunity to honor and celebrate the life, career and extraordinary scientific contributions of Bengt Robertson, MD PhD to neonatal medicine.

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His extensive work on surfactant biology, insights into neonatal lung physiology and mechanisms of lung injury contributed immensely to the development of surfactant therapy for preterm infants, including the original formulation of the surfactant, Curosurf (now called poractant alfa), which has had such a major impact on improving the outcomes of so many preterm infants. Beyond his renowned research related to the developing airway and epithelial biology, Dr. Robertson was also one of the early pioneers studying lung circulation in the fetus and newborn, including studies on vascular changes associated with congenital heart disease. In fact, his PhD thesis was entitled “Intrapulmonary arterial pattern in normal infancy and transposition of the great arteries” [1], in which he provided early insights into pulmonary artery structure as well as original work on the presence of intrapulmonary bronchopulmonary anastomoses (IBA), or “shunt vessels,” as investigated by microangiography and histology [2]. The implications and importance of these findings remain as major clinical challenges, especially in the setting of infants with developmental lung diseases, including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia and others [3]. Dr. Robertson’s early observations further reflect the depth of his understanding of the importance of the developing lung and its circulation, and early insights into the nature of neonatal pulmonary hypertension (PH), especially after preterm birth, which is the topic of this brief review.

Persistent Pulmonary Hypertension of the Newborn in Preterm Infants

At birth, the pulmonary circulation undergoes a remarkable transition from its high resistance and low flow state *in utero* to a low resistance and high flow circuit shortly after birth [4]. Such mechanisms as the loss of fetal lung liquid, rhythmic distension of the lung and increased alveolar oxygen tension lead to the release of endogenous vasodilators, including nitric oxide (NO) and prostacyclin (PgI_2) and reduced production of potent vasoconstrictors, such as endothelin-1 (ET-1) [5–7]. Persistent pulmonary hypertension of the newborn (PPHN) is characterized by the failure of this normal transition which leads to severe hypoxemia due to right-to-left shunting of blood away from the pulmonary circulation through the patent ductus arteriosus and foramen ovale. Over the past few decades, preclinical studies have explored diverse mechanisms that lead to high pulmonary vascular resistance (PVR) in PPHN, which include the inability to generate or sustain production of NO and PgI_2 and upregulation of ET-1 [7, 8]. Insights into mechanisms that contribute to regulation of pulmonary vascular tone and vasoreactivity during the perinatal period contributed to development of current PH-targeted drug therapies for acute respiratory failure in term newborns, including inhaled NO, sildenafil, ET-1 receptor antagonists and prostacyclin analogues, in order to improve oxygenation by reducing the extrapulmonary shunt due to high PVR, enhance right ventricular function and avoid need for more invasive therapies, especially extracorporeal membrane oxygenation [9–12].

Over the past 3 decades, these PH-specific agents, in combination with improvements in cardiovascular support, ventilator strategies and serial functional echocardiogram assessments, have markedly improved the clinical course and outcomes of term newborns with hypoxemic respiratory failure with PPHN physiology. Infants who fail these PH-targeted therapies often have such underlying problems as impaired cardiac performance often associated with systemic hypotension or high pulmonary venous pressures, inability to

optimize lung volumes and ventilation due to the severity of underlying lung disease (e.g., severe RDS, lung hypoplasia or others), or the diagnosis of genetic abnormalities of lung structure (such as alveolar capillary dysplasia, TBX4, NKX 2.1, surfactant protein disorders, and others).

Although most commonly recognized in term infants, the presence and management of PPHN and other issues as related to pulmonary vascular disease (PVD) in the preterm infant remain even more challenging. Although the abnormal transition of the lung with preterm birth is focused on the management of fundamental problems related to surfactant insufficiency, the need to support respiratory effort and achieve sufficient lung recruitment without inducing ventilator-induced lung injury and other respiratory complications, it is also clear that the failure of adaptation of the pulmonary circulation can further impair transition in preterm newborns as readily as in term newborns [13–15]. In fact, recent epidemiologic and physiologic studies have shown a far higher incidence of PPHN in preterm infants which has been strongly associated with the severity of prematurity [16, 17].

Historically, experimental studies have suggested that pulmonary vasoreactivity in response to high and low levels of oxygen to induce vasodilation or constriction, respectively, increase with advancing gestational age [4]. However, even extremely preterm lambs are already capable of regulating basal and stimulated pulmonary vascular tone through production of NO during mid-gestation [18] and are highly responsive to inhaled NO during mechanical ventilation after preterm delivery [19]. Clinical studies have further demonstrated that human preterm newborns often improve oxygenation in the setting of hypoxemic respiratory failure with PPHN during acute treatment with inhaled NO, especially in the setting of oligohydramnios and lung hypoplasia, supporting a key role for high vascular tone playing a central role in mediating elevated PVR [13–15]. In addition, lung pathology of preterm infants who die shortly after birth has shown that the respiratory severity score is strongly associated with hypertensive pulmonary vascular remodeling, further illustrating the potential contributions of early pulmonary vascular disease to severe RDS [15].

However, not all preterm infants with severe hypoxemia have demonstrable PPHN physiology as its underlying cause, suggesting that routine administration of pulmonary vasodilator therapies, including inhaled NO, without clear demonstration of underlying PPHN physiology is unlikely to be helpful in the management of hypoxemic infants. Multiple case series report marked improvement in oxygenation in preterm infants with PPHN [see 14], leading to consensus recommendations for inhaled NO use in preterms with PPHN physiology from a joint American Heart Association (AHA) and American Thoracic Society (ATS) guidelines working group, especially in the setting of oligohydramnios and prolonged preterm rupture of membranes [20]. However, our understanding of the potential benefits of inhaled NO or other PH-targeted drug therapies for the management of severe hypoxemia in preterm infants remains limited by the lack of relevant controlled trials that randomize subjects based on the presence of PPHN, as past studies that have used inhaled NO for the prevention of BPD did not differentiate between preterm infants with or without PPHN as part of their study design [21–23].

Interestingly, a retrospective study compared the outcomes of preterm infants who were identified as having the diagnosis of lung hypoplasia through a search of diagnostic codes through medical records at multiple institutions [24]. Overall, these infants had a high mortality rate with no effect on survival in subjects treated with inhaled NO. When further phenotyped as having lung hypoplasia with or without PPHN, however, these investigators reported that the use of inhaled NO led to a nearly 30% improvement in survival [24]. This subgroup analysis did not achieve statistical significance partly due to the small patient numbers or by sufficient verification of PPHN by echocardiogram in these subjects. Nevertheless, these interesting findings support the speculation that early identification and intervention, specifically in babies who have PPHN physiology who are prematurely-born can improve survival in this subpopulation.

Pulmonary Vascular Phenotypes of Prematurity

In addition to PPHN, work over the past decades has led to a growing understanding that PH, or more broadly, pulmonary vascular disease (PVD) in preterm infants, presents at different postnatal ages with variable severity, which has distinct implications for clinical management and risks for short and long-term outcomes. These can be partially characterized by the differences in postnatal timing and severity of PH, including early, late and chronic disease, which represent diverse pulmonary vascular phenotypes of preterm infants (Table). Insights into these different phenotypes is needed to better understand mechanisms underlying the pathophysiology of PH in these infants and the impact of PVD on disease course and outcomes, as based on the clinical setting and context in which PH has been diagnosed.

Delayed Vascular Transition—As discussed above, preterm infants can have clinical and echocardiographic evidence of supra-systemic PH in the hours and days after birth, in which infants have severe hypoxemia due to extrapulmonary right-to-left shunt (i.e., PPHN). In other infants, early echocardiogram findings of PH may represent the highly variable and delayed vascular transition (DVT) of the lung circulation in infants without sufficient severity of underlying PVD to cause severe hypoxemia yet the normal decrease in pulmonary artery pressure is slowed [16].

To explore the natural history of the transition of the pulmonary circulation at birth, a small cohort of preterm infants was studied with daily echocardiograms performed during the first 2 weeks of life [16]. In this study, Mirza and colleagues reported different patterns of postnatal changes in estimated pulmonary artery pressure, which often included subjects with mild but persistent elevations of pulmonary artery pressure, suggesting delays in the transition of the pulmonary circulation to normal postnatal values. Delayed vascular transition (DVT) defined by echocardiographic evidence of PH at 3–4 days of life in the absence of hypoxemic respiratory failure was reported in 55% of the cohort. PH resolved in most of these infants by 3–4 days of age and was labeled as “physiologic PH.” In 30% of the subjects, echocardiogram signs of PH persisted throughout the first 2 weeks of life. Overall, DVT was more frequent in the most premature infants and was associated with higher mortality and an increased risk for BPD. Whether or not early interventions in the subgroup of preterm infants with DVT would improve late outcomes remains worthy of study.

Early PVD in Preterm Infants

Bronchopulmonary dysplasia (BPD), the chronic lung disease that follows preterm birth, is characterized by an arrest of vascular and alveolar growth and high risk for PH, yet mechanisms contributing to its pathogenesis and early strategies to prevent BPD are poorly understood. In addition to its impact on developing PH, preclinical and clinical studies suggest that early disruption of angiogenesis during critical periods of lung vascular growth impairs alveolarization or growth of the distal airspace (the 'vascular hypothesis' of BPD) [25, 26]. Past studies demonstrate that early disruption of lung vascular growth due to hemodynamic stress *in utero* or by treatment with anti-angiogenesis agents during the early postnatal period causes PH and impairs alveolarization [27–29]. Brief treatment with angiogenesis inhibitors shortly after birth, including drugs that specifically target vascular endothelial growth factor-A (VEGF-A) signaling, cause severe PH that is sustained throughout infancy and into adulthood [29]. These studies further demonstrate that in addition to causing PH, early disruption of lung angiogenesis impairs alveolarization, suggesting an important role of vascular growth and signaling for normal development of the distal airspace. Most importantly, early autopsy studies clearly demonstrate decreased lung VEGF expression with striking evidence of lung simplification and a dysmorphic vasculature from human preterm infants dying with BPD, providing clinical evidence supporting the important role for angiogenesis in the pathobiology of BPD [26]. Preclinical studies further demonstrate that endothelial-derived products promote alveolar epithelial growth and septation, highlighting the important role of angiocrine signaling during normal lung development, as well as support for the hypothesis that early therapeutic strategies that preserve lung endothelial survival and function may decrease the risk of BPD.

Experimental studies support epidemiological findings that adverse intrauterine stimuli are sufficient to impair vascular growth and induce long-standing and severe PH independent of postnatal factors, including hyperoxia and ventilator-induced lung injury [30]. Furthermore, clinical studies have shown that abnormal placental vascular structure and evidence of placental hypoperfusion are strongly associated with neonatal outcomes of intrauterine growth restriction (IUGR) and high risk for development of BPD and BPD-associated PH [31, 32]. Prospective studies have shown that antenatal factors assessed on the first day of life [33, 34], cord blood biomarkers of impaired angiogenesis [35, 36] and early echocardiography findings of pulmonary hypertension shortly after birth are strongly linked to the risk of BPD, PH, prolonged NICU hospitalization and late respiratory outcomes in childhood [16, 37]. Thus, antenatal determinants not only cause abnormalities of short-term respiratory function, as reflected by the prolonged need for invasive ventilation and a more severe NICU course, but early injury *in utero* causes sustained disruption of lung and pulmonary vascular structure throughout infancy, reflecting the adverse effect of fetal programming [38–40]. Antenatal stresses, including chorioamnionitis and preeclampsia (with or without IUGR), in preterm neonates contribute to BPD risk [43, 44]. Data from animal models of mechanisms linking antenatal stress to BPD pathogenesis and late cardiorespiratory outcomes are limited, but recent studies suggest important mechanistic roles for disruption of hypoxia-inducible factor (HIF), insulin-like growth factor and VEGF signaling pathways [41, 42].

Clinically, echocardiography- confirmed signs of DVT and early PH are associated with a higher risk for the subsequent development of BPD, late PH and increased mortality [16, 37]. A prospective study demonstrated that early echocardiographic evidence of increased pulmonary artery pressure even without evidence of severe PH, RV dysfunction or severe hypoxemia at day 7 is strongly associated with high risk for subsequent development of BPD and its severity, the presence of PH at 36 weeks' PMA and prolonged respiratory disease during early childhood [37]. The combination of need for invasive ventilation and PH by echocardiogram at postnatal day 7 is especially strongly associated with late morbidities.

Thus, early PVD as demonstrated by echocardiographic signs of PH at day 7 of life may provide a useful "biomarker" for identifying preterm infants at high risk for developing severe BPD, late PH and chronic respiratory disease during early childhood. Whether therapeutic strategies of this subgroup of preterm infants, including PH-targeted drugs or other interventions, can reduce BPD or its severity remains speculative.

Late PH in Evolving or Established BPD

In the original description of BPD in 1967, Northway and colleagues report that "...(of infants with late deaths) all patients had striking cardiomegaly and right ventricular hypertrophy... (and that) the pathogenesis of cor pulmonale is puzzling...." [43]. PH has long been associated with poor survival in preterm infants with BPD even beyond the severity of underlying lung disease. A diagnosis of PH that persists beyond the first few months of life was linked with mortality rates as high as 40–50%, in 1980 [44], which is similar to a later study in 2007 [45]. Recent prospective studies show the presence of echocardiographic evidence of PH in 14–25% of preterm infants at 36 weeks' PMA, with especially high rates of PH identified in infants with severe BPD (range: 29–58%).[46–48].

Thus, despite major advances in perinatal and NICU care that has led to improved survival and changes in the nature of BPD over the decades, the diagnosis of PH and its management continue to be major challenges in infants with established BPD. In the setting of evolving or established BPD, PH is often clinically manifested by the sustained need for high levels of respiratory support, often with recurring cyanotic episodes. In some infants, the presence of PH with milder lung disease at the time of NICU discharge is often associated with high risk for progressive PH, perhaps related to late respiratory problems such as intermittent hypoxemia, obstructive sleep apnea, recurrent infections, chronic aspiration and other issues. Consensus recommendations from the AHA and ATS guidelines [20] and the Pediatric Pulmonary Hypertension Network [49] outline current strategies for the monitoring, evaluation and care of BPD-associated PH, but mostly acknowledge the need for further research to enhance outcomes.

Chronic PVD "across the lifespan"

Finally, there is a growing medical literature consistently demonstrating evidence of late echocardiographic markers of PH that persist throughout infancy, childhood and early adulthood [50]. Growing evidence for PVD in older children and young adults, or "*PVD across the lifespan,"* in which there has been growing evidence for high risk of development

of “borderline” PH and abnormal cardiac structure and function in young adults who were born preterm.

Although numerous studies have addressed the short-term and long-term effects of BPD on respiratory quality of life (QOL), few if any have accounted for the additive effects of PVD. Although not specific to BPD, QOL surveys of parents of children with PH who were treated with pulmonary vasodilators have found substantially lower QOL scores and higher parental stress, with scores even worse than those reported in children with cancer or congenital heart disease [51]. Limited data indicate that treatment of BPD-associated PH correlates with improvements in functional status and likely QOL. There is growing evidence that preterm infants with or without BPD may have evidence of subclinical PVD that persists into adolescence and adulthood. Echocardiographic markers, such as pulmonary artery acceleration time, indicate the presence of subtle PVD through childhood in preterm infants. By adolescence, mild elevations in mean pulmonary artery pressure are detected, which are highest in preterm-born adults with BPD. By right heart catheterization, adults who were born moderately to extremely preterm also have higher mean pulmonary artery pressure than those born at term [52]. Although most individuals in these studies fell below treatment thresholds, numerous studies now associate subclinical elevations in mean pulmonary artery pressure with increased overall mortality. Finally, RV function is a primary driver of overall function and QOL in preterm-born adults with PVD. Limited evidence demonstrates right ventricular dysfunction in preterm-born adults despite subclinical PVD, and thus potential for persistent impairment in QOL.

Conclusions and Implications

Thus, the overall goal of this review is to better define and characterize the distinct settings in which evidence of PH or PVD contributes to clinical disease after preterm birth, which have significant implications regarding diagnostic evaluations, therapeutic strategies, identification of preterm infants at risk for late cardiopulmonary disease and improving patient selection and therapeutic targets to enhance future randomized clinical trial design.

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TABLE 1.

Pulmonary vascular phenotypes of prematurity

• **Early (first 2 weeks of life)**
1) PPHN Syndrome: hypoxemic respiratory failure with supra-systemic PAP causing extrapulmonary right-to-left shunting of blood across the patent foramen ovale and/or ductus arteriosus;
2) Delayed pulmonary vascular transition: variable patterns of changes in estimated PAP in the absence of severe hypoxemia due to PPHN physiology, associated with higher risk for BPD and mortality;
3) Early pulmonary hypertension at postnatal day 7: as a “biomarker” for BPD, late PH and prolonged respiratory disease in early childhood.
• **Late (weeks to months after birth)**
1) Associated with evolving or established BPD, especially in infants with severe BPD, clinically characterized by sustained need for respiratory support and supplemental oxygen therapy, often with recurrent cyanotic episodes if severe;
2) Pulmonary hypertension after NICU discharge with persistent or late respiratory morbidities, such as intermittent hypoxia, obstructive sleep apnea, acute viral infections, aspiration and other stresses.
• **Chronic (months to years, or “pulmonary vascular disease across the lifespan”)**
1) Persistent subclinical echocardiogram abnormalities during infancy and childhood
2) May contribute to exercise intolerance
3) “Borderline” or mild elevation of pulmonary artery pressure reflecting pulmonary hypertension, with or without abnormal cardiac structure and function in prematurely-born adults.