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TOPICAL REVIEW

Long-term pulmonary vascular consequences of perinatal insults

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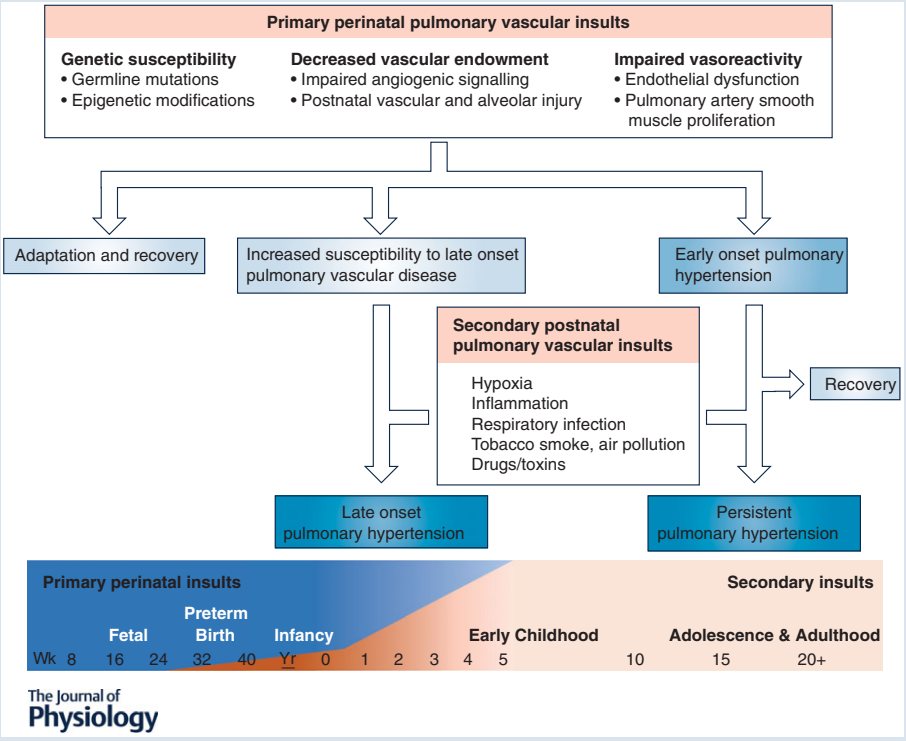

Abstract Development of the pulmonary circulation is a critical component of fetal lung development, and continues throughout infancy and childhood, marking an extended window of susceptibility to vascular maldevelopment and maladaptation. Perinatal vascular insults may result in abnormal vascular structure or function, including decreased angiogenic signaling and vascular endowment, impaired vasoreactivity through increased pulmonary artery endothelial dysfunction and remodeling, or enhanced genetic susceptibility to pulmonary vascular disease

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through epigenetic modifications or germline mutations. Although some infants develop early onset pulmonary hypertension, due to the unique adaptive capabilities of the immature host many do not have clinically evident early pulmonary vascular dysfunction. These individuals remain at increased risk for development of late-onset pulmonary hypertension, and may be particularly susceptible to secondary insults. This review will address the role of perinatal vascular insults in the development of late pulmonary vascular dysfunction with an effort to highlight areas of critical research need.

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Abstract figure legend Long-term pulmonary vascular consequences of perinatal insults. A number of insults may contribute to increased risk and development of overt pulmonary vascular disease. Additionally, severity, synergy and timing of insults may impact susceptibility to pulmonary vascular disease. Note preterm birth represents a unique overlap of primary and secondary insults.

Introduction

Although the development of pulmonary vascular disease (PVD) is thought to result from multiple converging insults, the role of perinatal pulmonary insults in driving long-term pulmonary vascular dysfunction remains poorly understood. A number of prenatal and postnatal vascular and alveolar insults may increase the later risk of developing PVD, even in the absence of clinically evident pulmonary vascular dysfunction in the neonate. The Barker Hypothesis, or the Developmental Origins of Health and Disease Hypothesis, was originally proposed to explain developmental priming of the cardiovascular system (Barker, 1995, 2007). However, its tenets are highly relevant to the developing pulmonary vasculature as well (Maron & Abman, 2017). Key concepts include the interplay between adaptive and maladaptive responses to environmental cues in a developmentally plastic host, effects of nutrition and fetal stress, and the role of epigenetic modifications (Wadhwa *et al.* 2009). This review will address the role of perinatal vascular insults in the development of late pulmonary vascular dysfunction with an effort to highlight areas of critical research need.

Normal vascular development

Development of the pulmonary vascular circulation is a critical component of fetal lung development, and occurs through both vasculogenesis and angiogenesis under highly regulated conditions (Peng & Morrisey, 2013; de Wijs-Meijler *et al.* 2017). Vasculogenesis is the process of blood vessel formation by *de novo* production of endothelial cells, giving rise to the heart and the first primitive vascular plexus within the embryo. Angiogenesis follows, and is responsible for the remodelling and expansion of the pulmonary vascular network through both endothelial sprouting and intussusceptive growth (Peng & Morrisey, 2013; Gao *et al.* 2016). During the canalicular stage of lung development (human gestation weeks 16–26), there is a dramatic rise in the number of lung capillaries to form the first air–blood interface, which continue to mature during the saccular stage (weeks 24–38). By the alveolar stage (week 36 through infancy), the immature double-capillary fetal network has fused to form a single capillary layer allowing for efficient gas exchange (Burri, 1999). From birth to adulthood, the pulmonary capillary surface area increases an additional 20-fold, and capillary volume increases 35-fold, forming an extensive pulmonary microvascular network. Finally, lung alveolar development is closely intertwined with vascular development, and a multitude of animal studies demonstrate that specific disruption of alveolar development impairs vascular development, and vice versa, confirming that early life alveolar disorders may also impair early pulmonary vascular development (Thebaud & Abman, 2007).

Impaired pulmonary vascularization

The role of prenatal pulmonary vascular insults

Impairments in angiogenic signalling during any of these critical windows of development can reduce pulmonary vascular density and ultimately total adult lung vascular endowment (Fig. 1). A number of prenatal conditions are characterized by impaired pulmonary angiogenesis signalling, including conditions of fetal insufficiency such as pre-eclampsia, fetal hypoxia and intrauterine growth restriction (IUGR), as well as inflammatory conditions such as chorioamnionitis and fetal infection, or from fetal drug and toxin exposure. Other prenatal conditions may also result in grossly abnormal structural development of the pulmonary vasculature, as seen in congenital diaphragmatic hernia and Down syndrome (Bush *et al.* 2017; Kardon *et al.* 2017).

Vascular endothelial growth factor A (VEGF) is a key regulator of pulmonary vascular development,

and its absolute requirement is demonstrated by murine studies showing lethality with targeted VEGF inactivation or knockout (Carmeliet *et al.* 1996; Ferrara *et al.* 1996). A number of studies have implicated impaired VEGF signalling and its receptor, excess soluble fms-like tyrosine kinase-1 (sFlt-1), in the pathogenesis of pre-eclampsia, a progressive multisystem disorder of pregnancy characterized by maternal and placental vascular dysfunction (Levine *et al.* 2004). The impaired placental vascular perfusion in these pregnancies further increases the risk for development of bronchopulmonary dysplasia and PVD after birth (Mestan *et al.* 2014).

Several conditions related to placental insufficiency may impair vascular development. For example, studies in IUGR sheep, most commonly defined as fetal weight below the 10th percentile for gestational age, demonstrate decreased fetal pulmonary alveolarization, stunted pulmonary vascular growth, and impaired *in vitro* pulmonary artery endothelial cell migration, tube formation and nitric oxide production (Rozance *et al.* 2011). Long term, a human twin study demonstrated that IUGR with a birth weight of less than 2500 g corresponded to a 43% increase in the hazard for developing PVD in adolescence or young adulthood (Class *et al.* 2014). Beyond placental insufficiency, fetal hypoxia can also drive impaired angiogenesis, and may result from residence at altitude, maternal tobacco use, or anaemia. Antenatal hypoxia results in a cascade of maladaptive consequences, including impaired angiogenesis and vascularization, endothelial barrier disruption and dysfunction, altered pulmonary vasoreactivity and decline in vascular resistance at birth, and pulmonary artery muscularization (Papamatheakis *et al.* 2013).

Finally, fetal inflammation and infection may affect vascular development, though the type and timing of inflammatory events appear to be important. For example, inflammatory mediators such as interleukin-6 in amniotic fluid or chronic low-grade infection with ureaplasma and mycoplasma are identified in a significant number of preterm births, yet these factors paradoxically decrease the risk for moderate to severe respiratory distress syndrome at birth, potentially by accelerating lung maturation (Watterberg *et al.* 1996; Hannaford *et al.* 1999; Shimoya *et al.* 2000). However, for the subset of preterm infants requiring mechanical ventilation, the risk for bronchopulmonary dysplasia is increased (Van Marter *et al.* 2002), suggesting amplification of the maladaptive response after fetal inflammatory priming (see Kramer *et al.* 2009 for additional review).

Effects of postnatal pulmonary vascular insults

Given that such a large component of pulmonary vascular development occurs after birth, infancy and childhood remain a window of susceptibility for abnormal development and overall endowment. Common direct postnatal vascular insults include premature birth, nutritional deficiency, hypoxia, inflammation, infection and environmental exposures such as cigarette smoke or air pollution. Importantly, postnatal pulmonary vascular insults may serve as the initial primary vascular insult, or alternatively as secondary insults in a vulnerable host, in which case they may further potentiate maldevelopment or maladaptation (Fig. 2).

Because they are born during a window of critical lung maturation (saccular stage), premature infants are

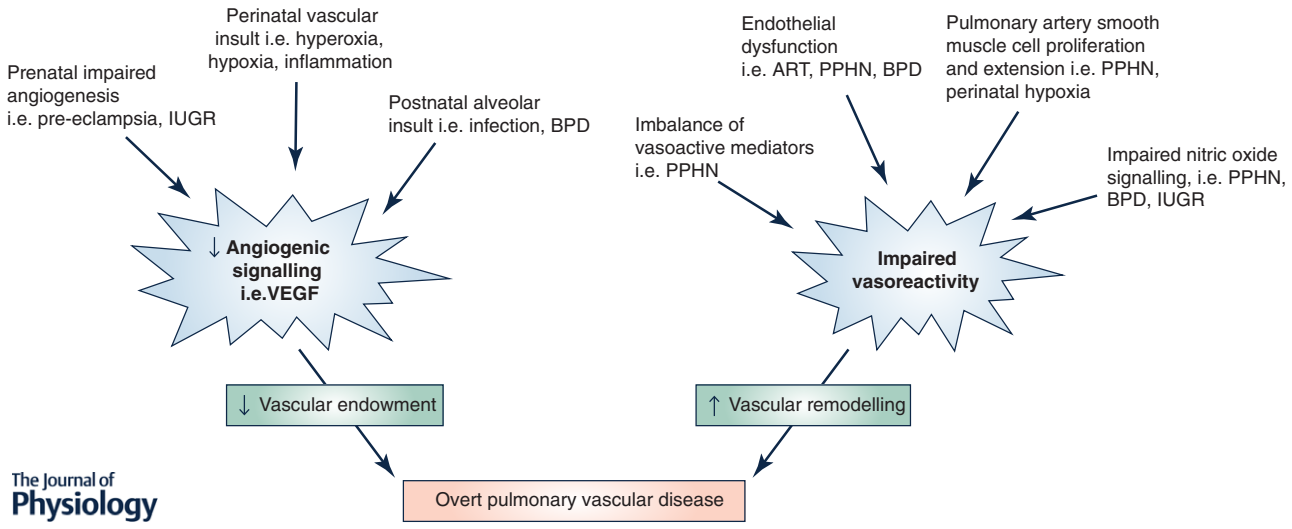

Figure 1. Perinatal pulmonary vascular insults contribute to late-onset pulmonary vascular dysfunction through multiple mechanisms
IUGR: intrauterine growth restriction. BPD: bronchopulmonary dysplasia. VEGF: vascular endothelial growth factor. PPHN: persistent pulmonary hypertension of the newborn. ART: assisted reproductive technology.

among the highest risk group for persistent pulmonary vascular injury. They have dramatically fewer vessels and higher pulmonary vascular resistance than those born at term, and are uniquely susceptible to further insults from mechanical ventilation, oxygen exposure, inflammation and infection (Bland *et al.* 2000). Those who demonstrate echocardiographic evidence of PVD at 7 days of age are at increased risk to develop bronchopulmonary dysplasia (Mourani *et al.* 2015), which is frequently considered a PVD in and of itself as it is characterized by significant vascular rarefication (Thebaud & Abman, 2007; Mourani *et al.* 2015).

Long term, preterm birth is associated with an 8.5-fold increased risk for developing pulmonary hypertension (defined as a mean pulmonary artery pressure $\geq$25 mmHg) in childhood and adolescence, and a 3.1-fold increased risk in adulthood, even after adjusting for confounding factors such as acute pulmonary disorders, congenital heart defects, congenital diaphragmatic hernia and chromosomal disorders (Naumburg *et al.* 2015, 2017). At rest, otherwise healthy young adults born preterm exhibit increased vascular stiffness with elevations in resting mean pulmonary arterial pressure (Goss *et al.* 2018). With graded exercise, adults born preterm demonstrate an exaggerated increase in pulmonary artery pressure (Laurie *et al.* 2018), though it is currently unclear if this is due to endothelial dysfunction such as impaired nitric oxide-mediated vasodilatation or due to a decreased capillary surface area available for recruitment.

Even infants born at or near term (alveolar stage) remain at risk for postnatal pulmonary vascular injury. Common insults in early life include respiratory infections and pulmonary over-circulation due to left-to-right shunts, which may be further exacerbated by exposure to hypoxia, hyperoxia or mechanical ventilation and worsening inflammation or oxidative stress (de Wijs-Meijler *et al.* 2017). Prolonged mechanical ventilation during the alveolar stage, even in the absence of hyperoxia or infection, can inhibit alveolar septation and impair angiogenesis signalling (Mokres *et al.* 2010). Left-to-right shunts, as seen in septal defects or patent ductus arteriosus, may accentuate pulmonary vascular sheer stress and promote vascular remodelling (Gao *et al.* 2016).

Potential for catch-up vascularization and lung growth

Each of these early insults results in a decreased pulmonary vascular density with potential to reduce the adult pulmonary vascular endowment (Fig. 2). The degree to which perinatal insults can be overcome by lung 'catch-up' growth is unclear. Individuals born premature or IUGR frequently demonstrate reduced spirometry throughout childhood and into adulthood. Although the data are predominantly negative, one study suggests lung catch-up growth in those who also demonstrated weight catch-up growth by age 5 (Friedrich *et al.* 2007; Kotecha *et al.* 2010; Vollsaeter *et al.* 2013; Suresh *et al.* 2015). Long term, distinct lung function trajectories develop during early childhood that are predictive of adult lung function and risk for adult lung disease such as chronic obstructive lung disease (Belgrave *et al.* 2018). However, most of these

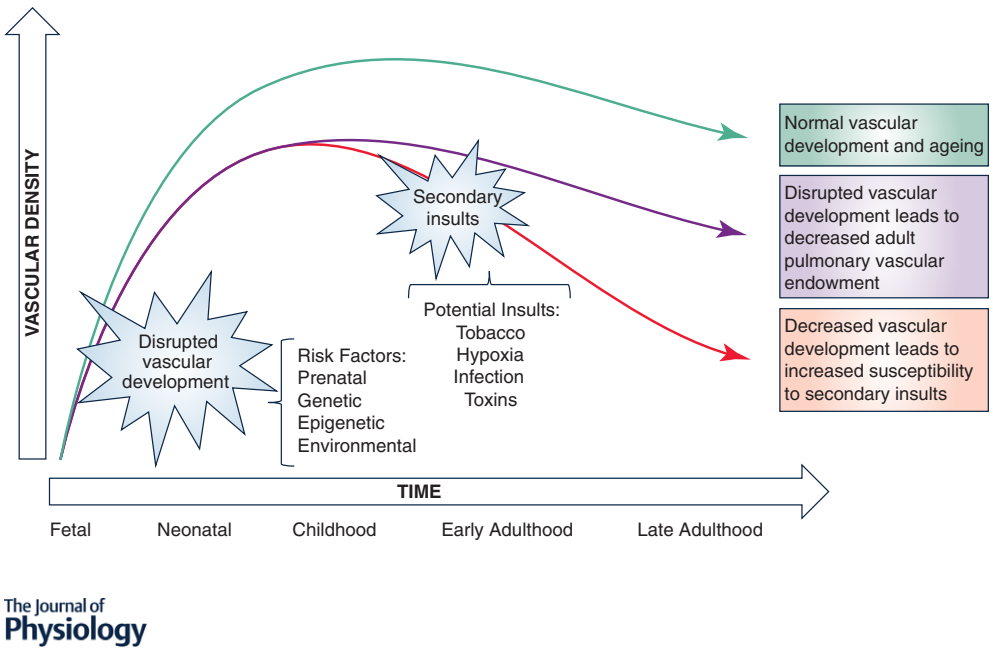

Figure 2. Impact of early pulmonary vascular insults on adult pulmonary vascular endowment and ageing

studies did not assess diffusion capacity or vascular density, and the effect on lung vascular growth is unclear.

Intriguingly, rodent studies of postnatal hyperoxia exposure, a commonly employed model of bronchopulmonary dysplasia, demonstrate a robust pulmonary vascular catch-up by 8 weeks of age, followed by severe vascular pruning when mice are aged beyond 1 year (Yee *et al.* 2011), which would suggest both catch-up potential as well as an accelerated ageing phenotype. Studies of pneumonectomy in adult rats demonstrate regenerative alveolarization in the remaining lung through angiocrine growth factors secreted by pulmonary capillary endothelial cells (Ding *et al.* 2011). The effectiveness of regenerative alveolarization in the setting of perinatal vascular insults and pulmonary endothelial dysfunction remains unclear. Endothelial progenitor cells are essential for vascular repair, and neonatal hyperoxia exposure also results in decreased pulmonary endothelial progenitor cells in the developing lung, increasing risk for development of bronchopulmonary dysplasia and pulmonary hypertension (Balasubramaniam *et al.* 2007). Whether decreased vascular density from a perinatal insult would impair such long-term regenerative capacity is unknown, but would add to the concern for an accelerated lung function decline with ageing.

The existence of long-term impairments in pulmonary vascular signalling merits further study. VEGF inhibition in adult rat models leads to air space enlargement, pulmonary vascular pruning and emphysema, suggesting ongoing need for VEGF signalling to maintain both alveolar and vascular structures (Kasahara *et al.* 2000). In a study of systemic microvascular density in human infants, 3-month-old offspring of hypertensive pregnancies had increased circulating anti-angiogenic factors and decreased vascularization (Yu *et al.* 2016). However, the degree to which VEGF and other angiogenic signalling is impaired later in life after perinatal insults remains unknown. While lung function studies in adults born premature offer conflicting evidence of an accelerated lung function decline, human studies evaluating adult pulmonary vascular density after early pulmonary vascular insults are lacking (Doyle *et al.* 2006; Vollsaeter *et al.* 2013). This is in part due to a still relatively small number of adult survivors of severe perinatal pulmonary vascular insults who are beyond their mid-twenties, when normal declines in age-related lung function begin. Therefore, there is a critical need to better understand the pulmonary vascular ageing process in these individuals.

Altered pulmonary vasoreactivity and function

Even in the absence of an interruption of normal pulmonary angiogenesis and development, a number of perinatal conditions may impair normal pulmonary vasoreactivity (Fig. 1). Normally at birth, there is a progressive fall in pulmonary vascular resistance, rise in systemic vascular resistance, and closure of fetal shunts such as the ductus arteriosus, resulting in a successful transition from fetal to postnatal circulation (Hillman *et al.* 2012). In the setting of persistent pulmonary hypertension of the newborn, the pulmonary vascular resistance remains abnormally elevated at birth, resulting in right-to-left shunting through fetal pathways and severe hypoxaemia. Mechanisms are multifactorial and include decreased vascularity, but also abnormal muscularization of the small pulmonary arteries and an imbalance of vasoconstrictive mediators (Murphy *et al.* 1981; Christou *et al.* 1997; Pearson *et al.* 2001). Although initially considered primarily a failure to transition from a fetal to a postnatal pulmonary circulation, the multifactorial nature suggests a more long-lasting imprint on the pulmonary vasculature. Indeed, a history of persistent pulmonary hypertension of the newborn is likely over-represented in childhood pulmonary hypertension registries, and is associated with significantly increased pulmonary vasoreactivity in adulthood (Sartori *et al.* 1999).

An emerging perinatal cause of long-term abnormal pulmonary vasoreactivity is assisted reproductive technology. Compared to control children, healthy children conceived with assisted reproductive technology demonstrated 30% higher pulmonary artery pressures and increased right ventricular dysfunction when acutely exposed to altitude (Scherrer *et al.* 2012; von Arx *et al.* 2015). Intriguingly, a 4-week pretreatment with the antioxidants Vitamin C and E improved endothelial function, evidenced by enhanced nitric oxide bioavailability, improved flow-mediated vasodilatation, and attenuated hypoxic pulmonary hypertension in these children, suggesting a component of reversible redox dysregulation (Rimoldi *et al.* 2015).

Finally, perinatal hypoxia exposure may also drive abnormal long-term vasoreactivity. In humans, a history of perinatal hypoxia increases susceptibility to pulmonary vascular dysfunction more than 6-fold in young adults living at high altitude (Julian *et al.* 2015). Intriguingly, a mouse study of perinatal hypoxia demonstrated persistent alteration in the nitric oxide–cyclic GMP pathway persisting into adulthood, which was ameliorated by treatment with inhaled nitric oxide during perinatal hypoxic exposure (Peyter *et al.* 2014). Given that more hypoxic neonates are being treated with inhaled nitric oxide, additional studies of its long-term effects on vascular function in humans are warranted.

Genetic predisposition and epigenetic modifications

Insults to the pulmonary vasculature may occur on a background of increased genetic susceptibility to PVD

(Austin & Loyd, 2014). For example, children with Down syndrome who die from cardiopulmonary disease exhibit abnormal pulmonary vascular development, including persistence of a double capillary network in the distal lung, increased pulmonary arterial smooth muscle thickness, and prominent intrapulmonary bronchopulmonary anastomoses (Bush *et al.* 2017). Other mutations, such as mutations in the gene encoding for bone morphogenetic protein receptor 2 (BMPR2), exhibit reduced penetrance, variable expressivity, and are insufficient for the development of PVD alone but may contribute greatly to the overall susceptibility to secondary insults.

Beyond germline mutations, epigenetic modifications such as DNA methylation and histone modifications likely play a critical role in imprinting the developing pulmonary vasculature. Specifically, differential hypermethylation of pulmonary artery smooth muscle cells leads to a deficiency in superoxide dismutase-2, creating a hyperproliferative, apoptosis-resistant vasculature, and is one potential mechanism for long-term perinatal priming of the pulmonary vasculature (Archer *et al.* 2010). In rats, offspring of mothers fed restrictive diets during pregnancy develop exaggerated right ventricular hypertrophy and hypoxic pulmonary hypertension, associated with altered lung DNA methylation. These effects are attenuated by administration of histone deacetylase inhibitors to offspring, or alternatively by administration of the nitroxide tempol to calorie-restricted mothers during gestation (Rexhaj *et al.* 2011). Whether these are targetable modifications of the genetic code to decrease susceptibility to secondary insults and late PVD in humans merits further investigation. However, early success in modulating alveolar development through maternal vitamin C supplementation in infants exposed to *in utero* tobacco smoke was recently demonstrated (McEvoy *et al.* 2017), and suggests at least the future potential to favourably modulate vascular development.

Effect of early pulmonary vascular insults on right ventricular development

The cardiac inflow tract, pulmonary vascular smooth muscle, and proximal vascular endothelium all arise from a common multipotent cardiopulmonary mesoderm progenitor *in utero*, and thus direct insults to the developing pulmonary vasculature could also serve as direct insults to the right ventricle (Peng *et al.* 2013). However, this hypothesis remains poorly studied. Overall, the best evidence for a shared insult is that of premature birth. Infants born preterm, even in the absence of clinically evident PVD, have a distinct cardiac structure characterized by increased biventricular hypertrophy, with the right ventricle more affected than the left (Aye *et al.* 2017). This persists into early adulthood when early impairments in right ventricular function are clinically detectable (Lewandowski *et al.* 2013*a*,*b*). In a rodent model of bronchopulmonary dysplasia using postnatal hyperoxia exposure, rats aged to 12 weeks develop an adaptive type of right ventricular hypertrophy and are more tolerant to secondary insults such as hypoxia exposure (Goss *et al.* 2015*a*,*b*). However, when rats are aged to 1 year, they develop a similar degree of right ventricular dysfunction as seen in humans, associated with impaired mitochondrial function and biogenesis. Since these changes occur in the absence of substantial deterioration in pulmonary vascular pressures, they suggest late transition to a maladaptive right ventricle (Goss *et al.* 2017). Whether the right ventricular dysfunction observed in humans and animal models is truly due to a direct and independent right ventricular injury, or is secondary to a lifetime of increased cardiac work from mild increases in pulmonary vascular compliance, merits further study.

Increased susceptibility to late pulmonary vascular insults

Clearly, perinatal pulmonary insults increase the risk to develop late PVD through a number of mechanisms. Given that the development of pulmonary hypertension is frequently thought to result from multiple insults to the pulmonary vasculature, these perinatal insults also increase the susceptibility to established later pulmonary vascular insults such as hypoxia, cigarette smoke, infections, drugs or toxins. Beginning in infancy, postnatal alveolar insults also drive the risk for pulmonary vascular dysfunction. For example, in rodent models of bronchopulmonary dysplasia, postnatal hyperoxia exposure results in an increased susceptibility to viral illnesses and cigarette smoke (McGrath-Morrow *et al.* 2011; Buczynski *et al.* 2013). In humans, lower respiratory tract infection in childhood is associated with increased airflow obstruction and chronic obstructive pulmonary disease in adulthood (Chan *et al.* 2015; Hayden *et al.* 2015). Early life lower respiratory tract infection therefore may be an unrecognized risk factor for later PVD as well. Additional childhood alveolar disorders are also associated with an increased risk for PVD with age. For example, severe asthmatics may have evidence of pulmonary vascular pruning (Ash *et al.* 2018), and adults with cystic fibrosis who develop pulmonary hypertension have significantly higher mortality (Hayes *et al.* 2014).

Secondary insults such as hypoxia are also important. Acutely, hypoxia exposure results in inhibition of pulmonary artery smooth muscle cell potassium channel activity, resulting in depolarization, calcium entry and ultimately hypoxic pulmonary vasoconstriction. Over time, the elevated calcium level promotes smooth muscle cell proliferation and hypertrophy, leading to increased muscularization and chronic vasoconstriction (Weir *et al.* 2005). Pathological conditions such as sleep disordered

breathing or high altitude exposure may activate these pathways. For example, children and adults born premature have a blunted hypoxic ventilatory drive making them at increased risk for intermittent nocturnal hypoxia due to sleep disordered breathing (Hibbs *et al.* 2008; Montgomery-Downs *et al.* 2010; Bates *et al.* 2014). Hypoxia is a well-established cause of pulmonary hypertension, and in rat models, adult exposure to hypobaric hypoxia following postnatal hyperoxia results in an exaggerated hypoxic pulmonary hypertension (Goss *et al.* 2015*a*).

Finally, there is concern for the effect of later exposure to pulmonary vascular toxins in individuals with a history of perinatal pulmonary vascular insults. For example, tobacco exposure results in pulmonary vascular remodelling in smokers, even prior to the development of clinical lung disease (Santos *et al.* 2002; Weissmann *et al.* 2012). Another significant unanswered question is whether stimulants may serve as secondary insults in at-risk children and young adults with attention deficit disorder, especially given the increased use and growing recognition of amphetamines as a cause of pulmonary hypertension (Zamanian *et al.* 2018), though this remains largely untested. The decreased vascular density, vascular remodelling and epigenetic modifications that follow perinatal pulmonary vascular insults likely make these individuals uniquely susceptible to stressors later in life, and future studies should address this potential synergy.

Knowledge gaps

A number of questions and research gaps regarding the long-term pulmonary vascular outcomes after perinatal insults remain (Fig. 3). First, there is a critical need to better understand the adaptive and maladaptive responses to perinatal pulmonary vascular insults. Whether the adaptive and regenerative capacity of the developing lung can be harnessed in childhood to improve vascularization and ultimately adult pulmonary vascular endowment remains to be seen. Modulating vascular angiogenesis will require careful study of safe therapeutic windows, given that mouse studies of VEGF overexpression have resulted in development of leaky capillaries and pulmonary oedema (Kaner *et al.* 2000). Second, longitudinal biomarkers are needed to identify individuals at high risk for late PVD. Given the prominent role that epigenetics likely play in modifying pulmonary vascular risk after early pulmonary insults, future studies are warranted to identify high-risk individuals for early intervention, limiting the morbidity and mortality of late PVD and right ventricular dysfunction. Third, a better characterization of the susceptibility to secondary insults for specific perinatal insults would allow for personalized risk avoidance. Fourth, there is a critical need to understand the role of perinatal pulmonary vascular insults on the pulmonary vascular ageing process, and slowing vascular ageing may also improve alveolar ageing. Finally, given the significant impact of right ventricular dysfunction on all-cause mortality, additional study of the effects of perinatal pulmonary vascular insults on the transitioning right ventricle are warranted.

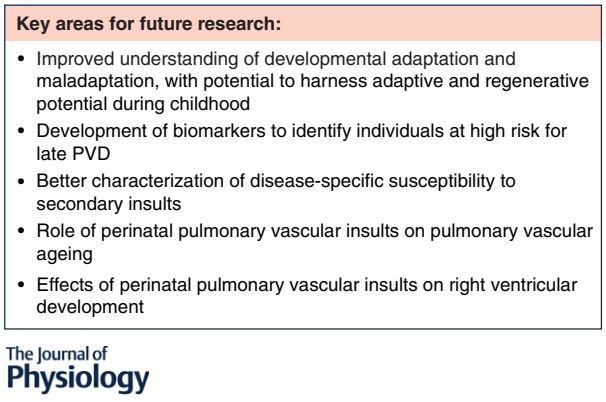

Figure 3. Current knowledge gaps

Conclusions

Based on the number of frequently concomitant perinatal pulmonary vascular insults, it is not surprising that one third of pediatric PVDs are considered multifactorial (del Cerro Marin *et al.* 2014). However, perinatal factors have not been assessed in adult pulmonary hypertension registry studies. In an age of personalized medicine, these factors truly deserve inclusion. Future studies should address both neonatal interventions to prevent early injury, as well as early diagnosis and management of high-risk individuals to prevent late morbidity and mortality. Given the remarkable improvements in neonatal care over the past several decades, resulting in growing numbers of infants with moderate to severe perinatal pulmonary insults now reaching early adulthood, the time is now.

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Additional information

Competing interests

None declared.

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