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Mini-symposium: Secondary Pulmonary Hypertension

Pathophysiology, screening and diagnosis of pulmonary hypertension in infants with bronchopulmonary dysplasia - A review of the literature

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EDUCATIONAL AIMS

- To describe the current understanding of the pathophysiology of pulmonary hypertension in infants with bronchopulmonary dysplasia.
- To describe the screening and diagnosis of pulmonary hypertension in the neonatal population with bronchopulmonary dysplasia.
- To propose, based on the current literature, an algorithm of evaluation and follow-up for screening and diagnosis of pulmonary hypertension in patients with bronchopulmonary dysplasia.

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SUMMARY

Bronchopulmonary dysplasia (BPD) is a common complication of extreme prematurity, which has increased over the last 20 years. BPD is associated with increased morbidities and mortality. It has been increasingly recognized that BPD affects overall lung development including the pulmonary vasculature. More recent studies have demonstrated an increased awareness of pulmonary arterial hypertension (PH) in BPD patients and recent international guidelines have advocated for better screening. This review will describe the current understanding of the pathophysiology of PH in infants with BPD, the in-depth assessment of the available literature linking PH and BPD, and propose an approach of screening and diagnosis of PH in infants with BPD.

INTRODUCTION

With the advent of new therapies and technologies, extremely premature infants are increasingly surviving. In the United States, for the year 2013, 1.4% of births were extremely preterm infants [2]. In 2014, 11.1% of Canadian preterm births were at 28 weeks of gestational age or less [3]. Despite strategies such as widespread use of antenatal corticosteroids, surfactant, gentle mechanical ventilation, and non-invasive ventilation, bronchopulmonary dysplasia (BPD) continues to be the most common complication of prematurity affecting up to 68% of the population born before 29 weeks of gestation [4]. BPD is associated with increased mortality, poor neurodevelopmental outcomes and long-term respiratory complications in survivors [5–7]. An abnormal pulmonary vascular component in infants with BPD has been increasingly recognized. However, the incidence of pulmonary hypertension (PH) is unknown since consensus is lacking regarding the best screening strategy for the detection of PH in this population. In this paper, we present a literature review on

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the lung development, the pathophysiology of PH in patients with BPD and a proposed algorithm for screening and diagnosis of PH in this population. Screening of PH in BPD patients has been recently endorsed in the consensus by the American Heart Association and American Thoracic Society on pediatric pulmonary hypertension [8].

BASIC PULMONARY EMBRYOLOGY AND PHYSIOLOGY

Anatomical pulmonary and vascular development

Pulmonary development has been traditionally divided in five major stages: embryonic, pseudoglandular, canalicular, saccular and alveolar [6]. Pulmonary circulation embryology is intrinsically linked to cardiovascular and pulmonary development. The pulmonary vasculature respects the same stepwise development of the lungs [9]. Macroscopic circulation (major arteries and veins) develops during the embryonic and pseudoglandular stages [9]. During the later, the microvasculature (capillaries) development occurs independently from the macrovasculature establishment [9]. The microvasculature stays poorly developed until the late canalicular to early saccular stage (26 weeks), following which it grows, tracking alveolar development [9]. During alveolarization, the initially thick interalveolar septa undergo progressive thinning and the double capillary layer merges into a unique single layer adult form [10]. Throughout development, the pulmonary vasculature progressively forms from hemangioblasts, dedicated to endothelial lineage, and align to form capillary structures into a delicate network intrinsically connected to the alveolar units [11]. Capillary segments run through the intra-acinar area of the lungs. The vascular wall within the lungs differentiates to give rise to pre- and post-capillary arteries, which have a different arrangement of smooth muscle cells with a transition from muscular to partially muscular to non-muscular segments with a progressive remodelling of vascular walls throughout pulmonary growth [11].

Impact of prematurity on vascular development

Normal lung development is variably disturbed depending on the degree of prematurity. Infants born at 24 weeks of gestation are in the canalicular phase, whereas with increasing weeks, patients tend to get closer to the saccular phase of pulmonary development [12]. Throughout those weeks, alveoli and capillaries begin their development, leading to a vast network of delicate alveolar-capillary units that will permit appropriate gas exchange. With prematurity, interstitial extracellular matrix remodelling is affected, causing deleterious impact on the natural thinning process that allows diffusion of gases in both directions [12]. Growth factors regulate both vascular and pulmonary structure development and differentiation, mediating interactions between epithelial, endodermal and mesenchymal cells [11,13]. Microvascular development has multiple steps, including endothelial cell differentiation, proliferation, migration, tube formation, branching, vessel remodelling, and maturation. The regulation of lung microvascular development requires the correct spatial and temporal expression of several angiogenic factors, all-needing to be perfectly orchestrated in the ideal environment (i.e.: oxygen tension) [14,15]. Expression of the various growth factors and their receptors is disturbed by the premature exposure to extra-uterine environment, and the injury by mechanical ventilation, inflammation and reactive oxygen species. As such, oxygen is only one of the many known factors to reduce Vascular Endothelial Growth Factor (VEGF) signalling, partly through its action on HIF, and to greatly impact the vascular development in premature infants [10].

BRONCHOPULMONARY DYSPLASIA

"Old" and "New" BPD

BPD was initially described by Northway *et al* in 1967 as fibroproliferative changes of the pulmonary parenchyma in neonates receiving aggressive mechanical ventilation [16]. With the significant advances that occurred in neonatal intensive care over the last 20 years, an increased number of extremely premature infants are surviving and the "new BPD" is characterized by simplification of the parenchyma with a paucity of alveolar structure and pulmonary vessels remodelling [17].

Definition of BPD

In 2001, the National Institute of Child Health and Human development (NICHD) Workshop on BPD agreed upon a definition stratified by gestational age at birth using a threshold of 32 weeks [18]. This definition is based on the evidence that oxygen needs at 36 weeks of corrected gestational age has been associated with long-term impairment in lung function [19]. In 2003, Walsh et al. proposed a physiological definition of BPD [1]. According to this definition, BPD is evaluated at 36 ± 1 weeks corrected age. Patients are diagnosed with severe BPD if still requiring mechanical ventilation, continuous positive airway pressure, or oxygen above 30%. Patients with oxygen needs below 30% are submitted to a stepwise oxygen reduction test. Infants that fail the test are diagnosed as moderate BPD [1]. This definition allows for easier measurement of BPD rates and for standardisation among trials because of the set saturation limits established by this definition.

Pulmonary parenchymal pathophysiology of BPD

The pathophysiology of BPD involves injury to the arborizing lung due to volutrauma, barotrauma, atelectrauma and biotrauma (toxicity by reactive oxygen species, infection and inflammation). Reactive oxygen species (ROS) disturb growth factor signalling, extra-cellular matrix assembly, vascular development, cell proliferation, differentiation and apoptosis. Hyperoxia is also known to increase the fragility of alveolar cells when exposed to mechanical strain, which causes shear stress, inflammation and cellular necrosis in the context of immature repair mechanisms [6]. Recently, it was shown in newborn mice exposed to hyperoxia that multiple sphingolipids (including ceramide) were highly expressed, leading to abnormal alveolar morphology and altered VEGF expression [20].

Pulmonary vascular pathophysiology of BPD

The environment greatly impacts the vascular development with oxygen, infection, hypoxia, and inflammation being injurious to the developing parenchyma and its associated vessels [21]. Regulation of pulmonary vascular tone is severely impacted in BPD by a reduced vascular surface, immature repair mechanisms, various inflammatory cytokines and the presence of overcirculation when there is a concomitant patent ductus arteriosus (PDA) [6]. Birth of VLBW infants during the canalicular and saccular stages of lung development appears to disrupt the normal program of alveolar and vascular development, resulting in the "new BPD," characterized by alveolar simplification, dysmorphic capillaries, and increases in vascular and airway smooth muscle cells. Abnormal deposition of the extracellular matrix (ECM) components (e.g., elastin and collagen) and interstitial fluid accumulation are also observed. Patients with BPD have a reduced expression of pro-angiogenic factors such as: vascular endothelial growth factor-B (VEGF-B), VEGF receptor-2 and angiopoietin receptor Tie-2 [21].