Preface

Neonatal Pulmonary Hypertension: Phenotypes, Physiology, and Management

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In the early 1970s, several case reports and series outlined neonates with cyanosis, respiratory distress associated with right-to-left shunt across the ductus arteriosus, right ventricular hypertrophy, and pulmonary hypertension (PH) diagnosed by cineradiography, ECG, or cardiac catheterization.[1,2] These infants had either parenchymal lung disease or pulmonary oligemia on chest radiograph and were called persistent pulmonary vascular obstruction in newborn[3] or persistent transitional circulation,[1] persistent fetal circulation, and subsequently, persistent pulmonary hypertension of the newborn.[4] During the subsequent years, the presence of acute PH was observed in preterm infants. Over the last 15 years, our understanding of the incidence, echocardiographic features, and management of early PH in extremely preterm infants continues to advance. Chronic PH is associated with conditions such as congenital diaphragmatic hernia (CDH) or bronchopulmonary dysplasia (BPD).

Instead of classifying neonatal PH based on infants' gestation, timing, or underlying disease, we prefer an approach using physiology to classify various phenotypes: resistance-driven, flow-driven, and postcapillary (**Fig. 1**). Such a physiologic approach guides therapeutic management. For example, inhaled nitric oxide (iNO) is indicated in resistance-driven PH but may worsen pulmonary edema in flow-driven and postcapillary PH. The increased availability of bedside echocardiography enables us to target therapy to individual patients ("precision-medicine" approach).

Previous clinical trials in neonatal PH have focused on hypoxemic respiratory failure with oxygenation indices as inclusion criteria and also as primary endpoints. This approach led to the inclusion of hypoxic preterm and term neonates secondary to

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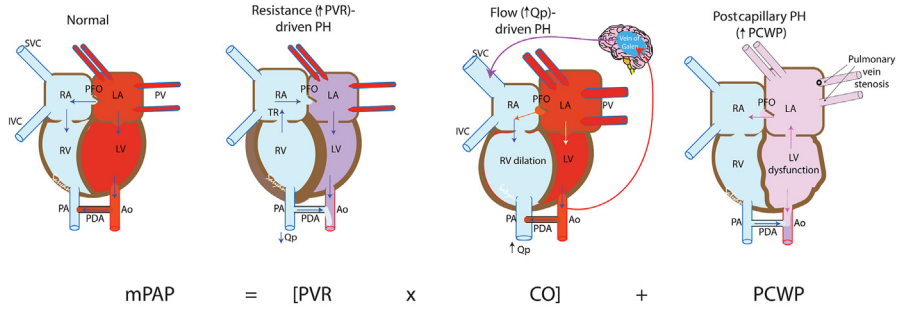

Fig. 1. Physiologic phenotypes of neonatal PH. Mean pulmonary arterial pressure (mPAP) is influenced by pulmonary vascular resistance (PVR), cardiac output (CO) or pulmonary blood flow (Qp), and pulmonary capillary wedge pressure (PCWP). Each of these components, PVR (resistance-driven PH), CO (flow-driven PH, as seen with vein of Galen and other left-to-right shunts), and PCWP (postcapillary PH secondary to left ventricular dysfunction or pulmonary vein stenosis) can contribute to elevated pulmonary arterial pressure. Therapeutic management is dependent on the phenotype. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TR, tricuspid regurgitation. (Image courtesy of Dr Satyan Lakshminrusimha.)

parenchymal lung disease, PH, cardiac dysfunction resulting in mixed results limiting clinical applicability. Future trials need to precisely identify the physiologic phenotype of neonatal PH to evaluate newer therapeutic options.

New insights into pathophysiology of neonatal PH, understanding the role of vascular mediators such as nitric oxide, prostacyclin, endothelin and oxygen free radicals, genetic and developmental pathways, and cardiopulmonary interactions have enabled us to advance diagnostic and therapeutic approaches.

Therapeutic management of neonatal PH has evolved from hyperoxia and alkalosis[5] and nonspecific intravenous pulmonary vasodilators, such as tolazoline.[6,7] The discovery of the key role played by endothelium-derived nitric oxide in normal pulmonary vascular transition at birth[8] led to the advent of iNO, a selective pulmonary vasodilator as a therapeutic agent, and revolutionized the management of neonatal PH.[9,10] However, high cost, lack of availability in some settings, and 10% to 15% incidence of poor or lack of sustained improvement to iNO have led to further investigation of pulmonary vasodilator therapy in neonatal PH. Enteral sildenafil has emerged as an effective alternate therapy of PH in resource-limited settings without access to iNO.[11] Newer therapeutic advances, such as newer prostacyclin analogs, endothelin antagonists, and soluble guanylate cyclase activators, may provide us with more tools to tackle iNO-resistant PH.

In this illustrated issue of the *Clinics in Perinatology*, internationally acclaimed authorities in the field of neonatal PH discuss pathophysiology, diagnosis, and management of neonatal PH secondary to parenchymal lung disease in both term and preterm infants, asphyxia, therapeutic hypothermia, CDH, BPD, and genetic and developmental lung disease in both high-income and low- and middle-income countries.

In addition to our appreciation of these authors, we would like to thank the editorial team at Elsevier, Mr Nitesh Barthwal, and Kerry K. Holland for their patience and support. We sincerely appreciate Dr Lucky Jain for assigning us with the important task of bringing out this issue dedicated to the management of neonatal PH.

With fond remembrance, we dedicate this issue in memory of Dr Regan Giesinger, our angel of Neonatal Hemodynamics. During her short life, she revolutionized the hemodynamic monitoring and finetuning of the management of neonatal PH. We both have shared panel discussions and state-of-the-art sessions with Regan and miss her astute observations and contributions to the field of neonatal PH. We feel honored to have an article authored by her as part of this issue of *Clinics in Perinatology*.

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