Pulmonary Hypertension and Pulmonary Vasodilators

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KEYWORDS

• Bronchopulmonary dysplasia • Congenital diaphragmatic hernia
• Echocardiography • Persistent pulmonary hypertension of the newborn
• Pulmonary vascular disease • Pulmonary vascular resistance

KEY POINTS

- Persistent pulmonary hypertension of the newborn is an acute perinatal condition with accepted clinical and echocardiographic criteria for diagnosis.
- There is limited validation for echocardiographic criteria for the diagnosis of pulmonary hypertension in infants after the acute transitional period.
- Cardiovascular comorbidities may be present in up to 50% of infants with bronchopulmonary dysplasia and pulmonary hypertension. Intervention may be necessary before or during treatment of pulmonary hypertension.
- There are no controlled studies supporting specific pulmonary vasodilator therapy for infants with pulmonary hypertension, but there are data to support specific dosing strategies for these children.

INTRODUCTION

Pulmonary hypertension (PH) in the perinatal period is often referred to as persistent PH of the newborn (PPHN). This diagnosis generally refers to the early, acute condition of systemic-to-suprasystemic pulmonary vascular resistance (PVR), with its attendant extrapulmonary right-to-left shunts and profound hypoxemia. PPHN may be transient, caused by metabolic derangements, or more persistent, most frequently in the setting of perinatal infection or lung disease. Further, with improvements in perinatal care, the increased survival of infants at risk for more chronic forms of PH, related to abnormal development of the lung and its vasculature, creates a different set of issues for providers, with assessments and treatment strategies that may differ from those that have

Conflict of interest and funding: The author has nothing to disclose.
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Clin Perinatol 43 (2016) 187–202
http://dx.doi.org/10.1016/j.clp.2015.11.013 **perinatology.theclinics.com**
0095-5108/16/$ – see front matter

evolved for the acute care of infants with PPHN. This article focuses on current issues in the evaluation and management of PH in the perinatal period, including assessment and initiation of chronic therapies, with most attention to infants with bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH).

DEFINITIONS AND CRITERIA FOR DIAGNOSIS OF PULMONARY HYPERTENSION

Older definitions of PH in predominantly adult patients were focused on an increase in mean pulmonary arterial pressure (P_{PA}) without evidence of significant left heart disease.[1] This definition was intended to identify patients with increased PVR caused by pulmonary vascular disease (PVD). However, because an increase in the pulmonary/systemic blood flow ratio (Qp/Qs) also affects the direct interpretation of the measurement of this value, the definition has been modified in children to include the assessment of PVR (normal, 1–3 Wood units $\times$ m^2)[2,3] as a better indicator of PVD. In the perinatal period, the timing of the usual transition to adult values for these parameters also needs to be considered, because term infants should reach these values by 2 to 3 months of age.[1,3] However, the transition for preterm infants is not as well defined.

Invasive Assessment of Pulmonary Hypertension: the Gold Standard

The only way to obtain direct measurements of pulmonary hemodynamic parameters is through cardiac catheterization. The hemodynamic criteria for the diagnosis of PH are:

- Mean P_{PA} greater than or equal to 25 mm Hg
- PVR greater than 3 Wood units $\times$ m^2
- Pulmonary capillary wedge pressure less than or equal to 15 mm Hg

To perform this procedure safely in any pediatric population, experienced personnel are required; serious complications from diagnostic catheterization in children with PH are uncommon (1%–3% of procedures) at experienced centers.[4,5] However, complications from cardiac catheterization may be more likely in small and ill children, particularly those with low birth weight (<2500 g).[6] Thus, catheterization is not frequently undertaken early in the course of neonatal illness (such as in the first month of life) unless complex congenital heart disease (CHD) potentially amenable to catheter-based intervention is present, and, if then, at a few experienced centers. Further, in interpretation of hemodynamic data from cardiac catheterization, therapies at the time of study need to be considered.

Cardiac magnetic resonance (MR) could supply much of the data that is obtained from cardiac catheterization, in a less invasive manner. However, there are limited validation studies for cardiac MR and diagnosis of PH in adults and none in infants.[7,8] Regardless, multiple factors may limit the application of this technology for assessment of PH:

- Transport to MR scanner and clinical management and sedation of a sick infant outside the intensive care unit or operating room
- Appropriate equipment and specialized expertise in cardiac MRI required to obtain sequences and interpret data
- Limitation of hemodynamic measurements: inability to assess the contribution of shunts, technical challenges in direct measurements with small infants

One report of cardiac MR for evaluation of CHD in infants showed a low rate of serious complications, comparable with reports on cardiac catheterization from experienced pediatric PH programs.[9]