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Mini-symposium: Biomarkers and Phenotype

Biomarkers for pediatric pulmonary arterial hypertension: challenges and recommendations

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EDUCATIONAL AIMS

THE READER WILL COME TO APPRECIATE THAT:

- Pediatric pulmonary artery hypertension (PAH) is rarer than adult PAH and in both cases the diagnosis is often delayed (with the exception of PAH associated with congenital diseases).
- The resulting right ventricle (RV) hypertrophy and eventual right heart failure from PAH is a cause of high mortality in both the adult and pediatric demographic.
- Biomarkers are a necessity as a diagnostic/prognostic adjunct in children with PAH given limitations with echocardiography and the risks associated with right heart catheterization.

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SUMMARY

Pediatric pulmonary arterial hypertension (PAH) is an uncommon disease that can occur in neonates, infants, and children, and is associated with high morbidity and mortality. Despite advances in treatment strategies over the last two decades, the underlying structural and functional changes to the pulmonary arterial circulation are progressive and lead eventually to right heart failure. The management of PAH in children is complex due not only to the developmental aspects but also because most evidence-based practices derive from adult PAH studies. As such, the pediatric clinician would be greatly aided by specific characteristics (biomarkers) objectively measured in children with PAH to determine appropriate clinical management. This review highlights the current state of biomarkers in pediatric PAH and looks forward to potential biomarkers, and makes several recommendations for their use and interpretation.

INTRODUCTION

Biomarker Definition

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to therapeutic intervention" [1]. Biomarkers are increasingly used in clinical research and practice as a diagnostic and/or prognostic adjunct. There is however, a constant need for evaluation of biomarkers to ensure accuracy and reproducibility of such outcomes. This review will consider the use of biomarkers in the pediatric demographic with pulmonary arterial hypertension (PAH) focusing on the biomarkers currently classified for PAH, their potential to ameliorate the disorder, and recommendations on how some challenges involving the application of biomarkers could be tackled.

Pulmonary Arterial Hypertension

PAH, a condition characterized by increased pulmonary arterial blood pressure and resistance in the arterial vasculature of the lung

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Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; IPAH, Idiopathic pulmonary arterial Hypertension; CHD, congenital heart disease; PVR, pulmonary vascular remodeling; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; RDW, red cell Distribution width; IL, interleukin.

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[2], may arise as an idiopathic disorder, or is often associated with secondary disorders [3]. PAH is a disease of many etiologies where the right heart and the lungs are adversely affected directly or indirectly through pathologies of other organs. The ensuing right ventricular (RV) hypertrophy and eventual right heart failure leads to high mortality [4]. The current accepted classification for pulmonary hypertension (PH) is provided in Table 1 [3]. The current clinical classification system categorizes PH into five groups with the most common form of pediatric PH falling in the category of Group I (PAH). This group accounts for approximately 90% of the incidence [5]. As in adults, the diagnosis of PAH in children is often delayed with the exception of PAH associated with congenital disorders [2]. Thus, the utilization of biomarkers that are sensitive, accurate, and reproducible has the potential to greatly improve early diagnosis, relevant prognosis, and more effective treatment in pediatric PAH.

PH Classification

For children with PH, the Netherlands data registry reported an incidence of 63.7 cases per million, with a majority of those cases belonging to PAH diagnosis (57.9 cases per million children) [6]. Although PAH in children is more rare than in adults, the incidence reported is comparable to the adult demographic with a reported incidence of 7.6 cases per million annually and a prevalence of 52 cases per million [7]. There is very limited data available on the registries with respect to pediatric PAH because of the smaller sample size of children with PAH and because of the lack of standardized assessment in early registries [8]. To overcome this, studies have been conducted to further our understanding of pediatric disease epidemiology data [9], and survival rates for children diagnosed with PAH have been reported in several studies [6,10]. Children are treated with either mono- or combination therapy, drug-specific therapy, treatment with calcium channel blockers, and bosentan [11]. A study conducted by the UK Pulmonary Hypertension Service for children [12] reports survival rates of approximately 90.5, 82.8 and 64.2% at 1, 3, and 5 years, respectively. Survival rates of 96, 84, and 74% for 1, 3, and 5 years respectively have recently been reported for children with IPAH/FPAH (familial) and APAH-CHD (associative) [13]. Similar studies further support these data [6,10,14]. There are data, however, that show differences in survival rates between children with IPAH compared with APAH [6,12,13]. Gender difference is an important factor for PAH in children, with higher occurrence observed in females than in males (2:1 ratio) [15].

Table 1
Current Classification for Pulmonary Hypertension [3]

1. Pulmonary Arterial Hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Heritable/familial (FPAH) 1.2.1. BMPR2
   1.2.2. ALK1, Endoglin
   1.2.3. Unknown 1.3. Drug and toxin-induced
   1.4. Associated with (APAH)
      1.4.1. Connective tissue disorders
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart diseases
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5. Persistent pulmonary hypertension of the newborn (PPHN)
1'. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension with left heart disease
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1. Chronic obstructive pulmonary disease (COPD)
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep disordered breathing
   3.5. Alveolar hyperventilation disorders
   3.6. Chronic exposure of high altitude
   3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with indistinct, multi-factorial mechanisms
   5.1. Hematological disorders (e.g. myeloproliferative disorders, splenectomy, hemoglobinopathies)
   5.2. Systemic disorders (e.g. sarcoidosis, pulmonary Langerhans cell histocytosis, lymphangiomatosis)
   5.3. Metabolic disorders (e.g. glycogen storage disease, Gaucher's disease, thyroid disorders)
   5.4. Others (e.g. tumoral obstruction, fibrosing mediastinitis, chronic renal failure and dialysis)

Right Heart Catheterization (RHC) is the gold standard for diagnosis of PH [16], which is defined (in part) as a mean pulmonary artery pressure of greater than or equal to 25 mm Hg. Typically, echocardiography (echo) is used as an initial screening tool, followed by RHC when pulmonary artery pressures are estimated to be elevated by echo [17]. Unfortunately in many cases, RHC fails to confirm a finding of PAH suspected by echo [18]. Biomarkers that would help inform the clinical decision to go/not go for RHC in the child with elevated pulmonary artery pressure as assessed by echo would greatly obviate unnecessary and expensive RHC (and the associated risks) for children who did not need it.

With therapy options more standardized for the adult PAH demographic, the therapeutic approaches to children with PAH can vary significantly depending on the experience of the clinical center and the medical team [19]. Although there are similarities in adults and children in terms of PAH pathobiology and patient response to therapeutic interventions [20–22], children are not small adults. Thus, the use of biomarkers in pediatric PAH should preferably be based on objective data in a systemized manner that incorporates etiology, developmental age, and gender differences with regard to prognostication, treatment, and evaluation of treatment efficacy. For this review, we have arbitrarily divided biomarkers for pediatric PAH into two classes: biochemical and imaging.

BIOCHEMICAL BIOMARKERS OF PULMONARY HYPERTENSION

Over the past several years excellent reviews on biomarkers and their application in PAH have been published [23–25]. However, these reviews have focused on adult PAH. The ideal biomarker for any disease would involve a measurement that is convenient, simple to perform, painless, and affordable, while offering high specificity and low incidences of false negatives and positives [2]. A superior biomarker (or set of biomarkers) would possess the aforementioned qualities while accommodating patient compliance when applied to the pediatric population.

PH is multifactorial with regard to pathobiology; as such, a single biomarker will not likely be 100% informative for the accurate diagnosis, relevant outcome and prognosis, and aspects of the underlying disease process. Thus, a combination of several biomarkers would be optimal for diagnostic and prognostic purposes. Current recommended guidelines apply the use of brain natriuretic peptide (BNP) and the N-terminal pro-BNP fragment as biomarkers for cardiac function [26] and mortality risk stratification [27]. Since natriuretic peptides were the early biomarkers used in PH, elevated levels of atrial natriuretic peptide (ANP) would serve as an important prognostic marker [26–29]. In addition, red cell distribution width (RDW), an emerging prognostic marker in PH, has been associated with poor survival [30]. Another lab parameter obtained is c-reactive protein (CRP), where it has been determined that elevated levels are associated with poor outcome