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Mini-Symposium: Secondary Pulmonary Hypertension

Diagnostics in Children and Adolescents with Suspected or Confirmed Pulmonary Hypertension

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EDUCATIONAL AIMS

The article will enable the reader:

- To provide a practical approach for the initial assessment and follow up of children with pulmonary hypertension (PH).
- To discuss the value of echo variables as diagnostic tools for assessment of pediatric PH.
- To provide a comprehensive overview of useful echo variables for estimation of right and left heart function in paediatric PH.

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SUMMARY

We provide a practical approach on the initial assessment and diagnostic work-up of children and adolescents with pulmonary hypertension (PH). Transthoracic echocardiography (TTE) often serves as initial study tool before invasive cardiac catheterization. Misinterpretation of TTE variables may lead to missed or delayed diagnosis with devastating consequences, or unnecessary invasive diagnostics that have inherited risks. In addition to clinical and biochemical markers, serial examination of patients with PH using a standardized TTE approach, determining conventional and novel echocardiographic variables, may allow early diagnosis and treatment in paediatric PH. Cardiac magnetic resonance imaging and computed tomography represent important non-invasive imaging modalities, that together with TTE may enable comprehensive assessment of ventricular function and pulmonary hemodynamics. Invasive assessment of haemodynamics (ventricular, pulmonary) and testing of acute vasoreactivity in the catheterization laboratory is still the gold standard for the diagnosis of PH and pulmonary hypertensive vascular disease (PHVD) in children and for the initiation of specific PH therapy. We suggest the regular assessment of prognostic TTE variables as part of a standardized approach for initial diagnosis of children with PH. Overreliance on any single TTE variable should be avoided as it detracts from the overall diagnostic potential of a standardized TTE examination for PH.

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INTRODUCTION

Pulmonary hypertension (PH) is a condition of multiple aetiologies, sharing a significant increase in pulmonary artery pressure. Pulmonary hypertensive vascular disease (PHVD) is characterized by progressive narrowing of pulmonary arterioles, abnormally high pulmonary vascular resistance (PVR), right ventricular (RV) dysfunction and left ventricular (LV) compression. Twenty-five to sixty percent of patients with pulmonary arterial hypertension (PAH) die within 5 years of diagnosis [1,2]. Paediatric PH is commonly characterized by the presence of precapillary PH due to increased pulmonary vascular resistance (PVR) and impaired blood flow just proximal to the pulmonary capillary [3]. In children, PAH (i.e. group 1 PAH of the Nice classification [4]) is a severe, usually progressive and life-limiting disease. As PAH is rare in childhood and single-center experience limited, diagnostic algorithms and implementation of protocols for disease monitoring are desirable to standardize medical care. This leads to a greater insight into disease progression, ultimately to achieve the best possible clinical outcomes. Consensus statements have been developed and recently published, specifically to guide the clinical care of children with PH [5,6]. The challenges of the diagnostic process, [7] treatment and follow-up [8] of children with PH include early detection in the absence of specific symptoms or markers, complexity of the underlying, often multifactorial, aetiologies and paucity of paediatric solid data to support and guide clinical management [9,10].

The content of this review comprises an abridged summary of the consensus statements for paediatric PH, in which specific topics are illustrated in far greater detail [5]. The aim of this review is to provide a short practical overview over the diagnostic work-up, monitoring and outpatient care of children and adolescents with PH, PAH, or PHVD. Transthoracic echocardiography (TTE) is, among many other non-invasive parameters, the most accessible non-invasive diagnostic means, not only for the initial confirmation of suspected PH but also for screening children at increased risk for PH development. Due to the variable body size and differences of underlying pathophysiology, TTE variables used for the assessment of paediatric PH can have different age-related reference ranges and variables impact on the accuracy of diagnosis in children vs. adults [11,12]. The gold standard for the initial diagnosis of PH remains an invasive evaluation, where in children with suspected PH, a right heart and left heart catheterization is recommended. Due to technical pitfalls impacting on data accuracy and associated procedural risk, invasive haemodynamic evaluation should be performed in experienced centers only.

PH CLASSIFICATION

In children, PH is evident with a mean PA pressure (mPAP) $\geq$ 25 mmHg when over 3 months of age at sea level [3,7]. During the World Symposium of Pulmonary Hypertension in Nice 2013 a new subgroup of 'multifactorial PH' was introduced to account for the heterogeneity of paediatric PH and special considerations that apply to children [4]. The term paediatric "PAH" (i.e., group 1 PH) defines a subgroup of pre-capillary PH with an end-expiratory pulmonary artery wedge pressure (PAWP) $<$ 15 mmHg and a PVR indexed to body surface area $>$ 3 WU $\times$ m^2. In 2011, the Pulmonary Vascular Research Institute (PVRI) introduced the disease entity "paediatric PHVD" (mPAP $\geq$ 25 mmHg; PVR index $>$ 3 WU $\times$ m^2), which was divided into 10 main categories (Panama Classification, 2011) [13]. This new Paediatric Panama classification was proposed in 2011 (Table 1) and takes into account perinatal maladaptation, insufficient development and pulmonary hypoplasia. The most common type of PH diagnosed in childhood is PAH associated with congenital heart disease (CHD) [14]. Untreated idiopathic PAH (IPAH) results in death within 2-3 years in adults and within 1 year after diagnosis in children [15], indicating that early diagnosis and early, sufficient (probably combination) PAH-targeted therapy is essential.

Table 1
'Panama classification' (2011): Basic categories of Paediatric Pulmonary Hypertensive Vascular Disease (Paediatric Taskforce of the Pulmonary Vascular Research Institute) (modified from: Cerro MJ, et al. Pulm Circ 2011; [13]).

Category	Description
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated paediatric pulmonary hypertensive vascular disease (isolated paediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Paediatric lung disease
8	Paediatric thromboembolic disease
9	Paediatric hypobaric hypoxic exposure
10	Paediatric pulmonary vascular disease associated with other system disorders

DIAGNOSTIC FEATURES

Ideally, children with suspected PH should be referred to, evaluated and treated in multidisciplinary, specialist paediatric PH centers. Ideally invasive assessment of cardiac hemodynamics should be performed prior to the initiation of therapy by means of TTE [16], cardiac catheterization [17], and cardiac MRI [18]. While the definite diagnosis of PH and PHVD is currently made by cardiac catheterization [17,19], the first and most frequently applied diagnostic modality in suspected PH is the TTE [5,7]. A comprehensive medical history and thorough physical examination are mandatory in the initial evaluation of PH. Further basic diagnostics and investigations usually include determination of the functional class (Table 2), electrocardiogram, chest $\times$ ray, and further functional tests (lung function test, 6 minute walk test (6MWT) and cardiopulmonary exercise test) in capable patients.

FUNCTIONAL CLASSIFICATION

The two most frequently employed functional classification (FC) schemes are the WHO and the New York Heart Association classification [20]. Functional classifications are, however, not without problems, particularly in very young children and children whose development may be abnormal due to associated syndromes or other developmental delays. The PVRI Paediatric Workforce recently suggested a specific FC system, adjusted for the use in infants and young children for different age groups, implementing factors such as the ability to thrive, including developmental milestones and school/nursery attendance (Table 2) [21]. Despite its recognized problems, WHO FC has been demonstrated as one of few convincing prognostic factors in a recent meta-analysis [22].

CHEST X-RAY

A baseline chest x-ray (CXR) often proves to be useful. In patients with PH, typical findings are central pulmonary artery dilatation, pruning (suggestive of loss of peripheral blood vessels), as well as right atrial (RA) and right ventricular (RV) enlargement in patients with advanced disease. However, the absence of signs of PH on a CXR does not rule out the diagnosis. Regular repeat CXRs at follow-up are not indicated, unless there is a specific clinical indication. A CXR is not sufficient to evaluate disease severity [20].