Editorial

Left Ventricular Diastolic Dysfunction in Pediatric Pulmonary Hypertension

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Pulmonary hypertensive vascular disease (PHVD) is characterized by progressive narrowing of pulmonary arterioles, abnormally high pulmonary vascular resistance (PVR), right ventricular (RV) dysfunction, left ventricular (LV) compression, and death in ≈25% to 60% of patients with pulmonary arterial hypertension (PAH) 5 years after diagnosis.[1,2] Meanwhile, consensus statements have been developed in North America and Europe specifically to guide the clinical care of children with pulmonary hypertension (PH).[3,4] The challenges in the diagnosis[5] and treatment[6] of pediatric PH include early detection in the absence of specific symptoms or biomarkers, the complexity of the underlying etiologies, broad comorbidities, genetic syndromes, and the paucity of pediatric trial data to support and guide clinical management.[7,8]

See Article by Burkett et al

The estimated prevalence of PAH is 2 to 16 cases per million children.[9–11] Children diagnosed with PAH associated with congenital heart disease and those with idiopathic/heritable PAH have a similar 5-year mortality in North America (29% versus 25%; REVEAL registry).[1] Untreated idiopathic PAH results in death within 2 to 3 years in adults and within 1 year after diagnosis in children,[12] indicating that early diagnosis and early, sufficient (probably combinatory) PAH-targeted therapy is paramount.

In children, PH is evident with a mean PA pressure ≥25 mm Hg when over 3 months of age at sea level.[5,13] The term pediatric PAH (ie, group 1 PH) defines a subgroup of precapillary PH with an end-expiratory pulmonary artery wedge pressure (PAWP) <15 mm Hg and a PVR indexed to body surface area >3 WU m^2. In 2011, the Pulmonary Vascular Research Institute introduced the disease entity pediatric PHVD (mean PA pressure ≥25 mm Hg; PVR index >3 WU m^2) that was divided into 10 main categories (Panama Classification, 2011).[14]

The invasively measured PAWP is a surrogate for the pressure in the large pulmonary veins, and thus, the mean left atrial pressure in most instances, but not necessarily the pressure in the pulmonary capillaries. Historically, an increased mean PAP defines PH, and PAWP has been used to distinguish precapillary PH (ie, PAH) from postcapillary PH in left heart diseases. The latter includes common adult heart failure with preserved ejection fraction, with increased LV end-diastolic and left atrial pressure, and optional RV dysfunction. More recently, 2 key points in the pathophysiology of PH/PHVD have been realized: (1) diastolic PAP is independent of RV stroke volume (which declines in advanced PAH), and thus, today, the diastolic transpulmonary pressure gradient is used to distinguish passive PH (postcapillary PH; diastolic transpulmonary pressure gradient <7 mm Hg in adults) from reactive PH/PHVD (ie, combination of pre- and postcapillary PH, with diastolic transpulmonary pressure gradient ≥7 mm Hg or PVR >3 WU in adults).[2,15] (2) Through ventricular interdependence, especially in systemic or suprasystemic PAH (RV pressure > LV pressure), not only RV but also LV diastolic dysfunction is evident, leading to left atrial pressure elevation, as well as decreased LV inflow and ejection, irrespective of the decreased pulmonary blood flow in the high PVR setting.[15]

Although the definite diagnosis of PH and PHVD is currently made by cardiac catheterization,[15,16] magnetic resonance imaging and chest computer tomography have become essential noninvasive imaging modalities in the management of PH.[17] However, the first and most frequently applied diagnostic test in suspected PH—beyond history taking, clinical examination, ECG, chest x-ray, blood plasma/serum N-terminal prohormone of brain natriuretic peptide—is the transthoracic echocardiogram.[3,5] Echocardiography in children usually allows a comprehensive assessment of the cardiovascular anatomy; it may also confirm RV or PA pressure elevation by Doppler interrogation of more than trivial tricuspid and pulmonary regurgitation and analysis of the end-systolic shape of the interventricular septum.[18] Nevertheless, over-reliance on a single echocardiographic variable and false estimation of RV systolic pressure because of poor CW-Doppler envelopes or severe tricuspid regurgitation can limit the value of the methodology for non-PH experts.[18] More novel, potentially prognostic echocardiographic variables to assess RV/LV geometry/function and RVP or PAP in pediatric PH include RA size[19,20]; tricuspid annular plane systolic excursion[21]; RV outflow tract velocity time integral; trivial tricuspid/RVOT velocity time integral ratio[22]; pulmonary regurgitation velocity; RV size[20]; LV size, LV end-systolic eccentricity index, end-systolic and end-diastolic RV/LV ratio[23]; RV stroke work[24]; LV strain and strain rate[25]; RV systolic/diastolic duration ratio[26]; and pulmonary artery acceleration time (Koestenberger M, MD, unpublished data, 2016). A combination of the above variables can help the clinician avoid some of the pitfalls of the echocardiographic examination at initial diagnosis and serial

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investigation of infants and children with PH.[18] Although ventricular–ventricular interactions are well recognized in conditions such as pressure overload or arrythmia, they have not been well studied in children with PAH, including those with congenital heart disease.

In this issue of *Circulation: Cardiovascular Imaging*, Burkett et al[27] present the results of a 2-center, prospective, ventricular function study combining conventional (B-mode, Doppler), biventricular deformation imaging and tissue Doppler imaging and near-simultaneous cardiac catheterization in 54 pediatric PH patients and in 54 age-, sex-, and institution-matched controls. All PH children underwent right heart catheterization at diagnosis or follow-up and were classified as having precapillary PH (here, mean PA pressure ≥25 mm Hg and PAWP <15 mm Hg). No controls underwent cardiac catheterization. A deformation imaging (speckle tracking) study on the identical cohort of pediatric PH patients had identified decreased systolic LV strain/strain rate, predominantly within the septum, with relationships to invasive hemodynamics, RV strain, and functional PH measures.[25]

In the current study,[27] the authors aimed to study the impact of pulmonary hemodynamics and ventricular interdependence on LV diastolic function in pediatric PH. By doing so, they directed their focus beyond RV systolic dysfunction that is known to determine clinical outcome but often is a late finding, particularly in younger patients, and even in those with advanced PAH. Burkett et al[27] show that children with PH exhibit LV diastolic dysfunction most consistent with impaired LV relaxation and decreased myocardial deformation, related to invasive hemodynamics, leftward septal shift, and prolonged RV systole. There were no statistically significant differences in diastolic measures between patients with and without a shunt, and minimal differences between patients with and without congenital heart disease. Multiple echocardiographic LV diastolic variables had weak to moderate correlations with invasively determined PH severity, leftward septal shift, and prolonged RV systole. A strength of this study is its design, in particular, the prospective data collection and the near-simultaneous echocardiographical data acquisition with invasive hemodynamics, in 2 of the leading PH centers in North America. The patient number is high when compared with similar pediatric studies previously published.

Of note, all of the PH patients had been intubated and ventilated during cardiac catheterization and echocardiography—an approach that is not followed by many PH centers, and is not recommended by the European Pediatric Pulmonary Vascular Disease Network in most instances,[15] because of the artificial hemodynamics and the risk of cardiovascular collapse with general anesthesia in PH patients.[16] The lack of both a standardized anesthesia protocol and a complete left heart hemodynamics (PAWP but not always left atrial pressure, LV enddiastolic pressure) may have had impact on the data gathered, but anesthesia probably have influenced both invasive and noninvasive data in a similar way.

Taken together, this prospective study is the first to describe near-simultaneous invasive and echocardiographical findings of LV diastolic dysfunction and highlights the occurrence and importance of RV–LV interaction in pediatric PH. To date, RV–LV interactions are not commonly assessed in clinical practice or mentioned in guidelines. Impaired LV filling likely contributes to impaired LV stroke volume and, hence, cardiac output, and the current article emphasizes the need to assess this better in children and adults with PAH. Although foremost emphasis is placed on RV systolic dysfunction in PAH, diastolic dysfunction, and in this particular study,[27] LV diastolic function, is abnormal and may be important to clinical outcome.

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Disclosures

Dr Hansmann indicates no conflict of interests related to the content of this article. Dr Hansmann is the current chair of the AEPC Working Group "Pulmonary Hypertension and Heart Failure" and the founding chair of the European Pediatric Pulmonary Vascular Disease Network (http://www.pvdnetwork.org).

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