

Comprehensive Noninvasive Evaluation of Right Ventricle-Pulmonary Circulation Axis in Pediatric Patients with Pulmonary Hypertension

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Abstract

Purpose of review The purpose of this review is to detail the advanced echocardiographic studies that evaluated outcomes in pediatric PH using these advanced imaging techniques: (1) right heart size and function (using 2D and 3D echocardiography), (2) myocardial mechanics, and (3) right ventricular (RV) to pulmonary arterial coupling.

Recent findings Advanced echocardiographic imaging tools in pediatric PH include RV/left ventricular ratio, 3D echocardiographic assessment of RV volumes and ejection fraction, right atrial and RV strain, and RV-pulmonary arterial coupling ratio that allow for evaluation of clinical outcomes in this patient population. The right atrial to RV axis provides insights to RV diastolic function that has been poorly understood in pediatrics. The RV-pulmonary arterial coupling ratio helps us understand the mechanics of the RV response to afterload.

Summary The advanced imaging tools provide clinical outcome evaluation in pediatric PH patients and provide insight into the RA-RV axis and the RV-pulmonary circulatory unit.

Introduction

Echocardiography is the most important noninvasive tool that is used as a routine assessment of pediatric pulmonary hypertension (PH) [1••, 2••, 3, 4•, 5, 6•]. It is used in screening as well as for continued follow-up and medication management [7•]. Conventional imaging includes assessment of anatomy in two-dimensions (2D), hemodynamics via Doppler echocardiography, and qualitative and quantitative evaluation of right ventricular (RV) and left ventricular (LV) function [3, 4•, 5, 7•, 8•, 9••, 10]. The advanced imaging tools in echocardiography include evaluation of right heart size and function, myocardial mechanics, and RV to pulmonary arterial (PA) coupling ratio [11–13, 14•, 15]. In recent years, different echocardiography parameters have been identified to be useful in identifying high-risk patients who are likely to develop adverse clinical outcomes [14•, 16•, 17, 18•, 19]. In this review, we will discuss the echocardiographic studies that evaluated outcomes in pediatric PH using these advanced imaging techniques: (1) right heart size and function (using 2D and 3D echocardiography), (2) myocardial mechanics, and (3) RV to PA coupling.

Right heart size and function using 2D and 3D echocardiography

Echocardiographic assessment of right heart size and function can be performed by 2D and 3D

echocardiography based on the recent adult and pediatric guidelines [9••, 20••]. Ryan et al. in 1985 derived the eccentricity index to differentiate between volume overload and pressure overload and found that LV deformation of the interventricular septum was greatest in end-systole in patients with RV pressure overload [21]. Eccentricity index > 1 has been shown to correlate well with invasive measurements of pulmonary artery pressure and to be a predictor of adverse outcome in adults [21]. Based on the concept of eccentricity index and septal shift, a RV/LV ratio in end systole to incorporate the RV in pediatric PH patients was derived (Fig. 1a) [22•]. This study compared 80 normal pediatric patients with 84 abnormal pediatric PH patients. RV/LV ratio in end-systole was higher in PH patients compared to controls and RV/LV correlated with hemodynamic measurements in catheterization within 48 h of cardiac catheterization [22•]. RV/LV > 1 was associated with an increased risk for an adverse event including initiation of intravenous prostacyclin therapy, atrial septostomy, death, or transplantation [22•]. For every increase of 0.1 units in RV/LV ratio, the hazard increased by 10% [22•].

With the advent of 3D echocardiography, RV volumes and function (Fig. 1b) can be measured more accurately to encompass the difficult geometric RV shape. RV volumes and function have been shown to

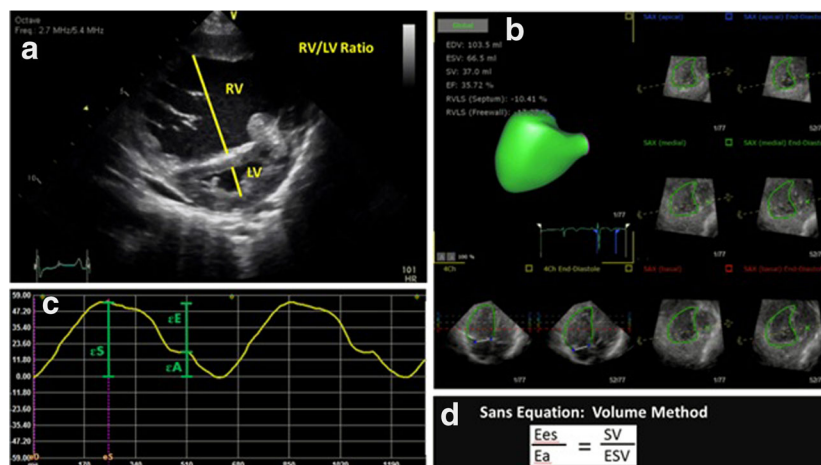


Fig. 1. Advanced echocardiographic imaging in pediatric pulmonary hypertension. **a** The right ventricular (RV)/left ventricular (LV) ratio. **b** Three-dimensional imaging of the RV: volumes, ejection fraction, and strain are shown in the pediatric pulmonary hypertension patient. **c** Right atrial function: ϵS = reservoir function, ϵE = conduit function, and ϵA = pump function. **d** Sans equation simplifies the RV-pulmonary arterial coupling ratio (E_{es}/E_a) into a volumetric method of stroke volume (SV)/end-systolic volume (ESV).

correlate well to cardiac magnetic resonance imaging (CMRI) with some underestimation of RV volumes [9••, 23, 24•]. Both normal values of RV volumes and function have been reported in adults and pediatrics [25, 26•]. Emerging studies have confirmed the prognostic value of 3D-derived RV volumes and ejection fraction (EF) in patients with PH and RV dysfunction [14•, 27•]. In a study with 96 pediatric PH patients compared to 40 normal controls, the PH patients had higher RV volumes and lower RVEF compared to controls [14•]. The RVEF had the highest area under the curve (0.83, with sensitivity of 90% and specificity of 67% with a RVEF cut-off value of 43%) [14•]. And when comparing to conventional indices of RV function such as tricuspid annular plane systolic excursion (TAPSE), the RV volumes and EF were prognostic in evaluating clinical outcomes whereas TAPSE was not prognostic [14•]. Nagata et al. found similar results in adult studies that RVEF was independently associated with cardiac outcomes in patients with diverse backgrounds and that RVEF offered incremental value over clinical risk factors and other conventional echocardiographic parameters for predicting future adverse outcomes [27•].

Right heart myocardial mechanics

Speckle tracking has become a clinical standard for assessing RV systolic function from a RV-focused apical view. Strain measures myocardial deformation whereas its time derivative, strain rate, defines the rate of deformation of myocardium over time. RV regional and global strain can be measured. Normal values of adult and pediatric RV strain have also been reported [9••, 28, 29, 30•, 31]. In 575 adult patients with known or suspected PH, Fine et al. demonstrated that RV strain was a strong predictor of survival even after adjusting for pulmonary artery pressures, pulmonary vascular resistance, and right atrial pressure [32•]. RV longitudinal systolic strain provided incremental prognostic value over conventional clinical and echocardiographic variables [32•]. Hardegree et al. showed that RV free wall longitudinal strain can be used as a quantitative assessment of RV systolic function in adult PH patients and that an improvement of RV systolic strain $\geq 5\%$ while on therapy was found to be an independent predictor of improved survival [33]. Okumura et al. subsequently demonstrated in pediatric idiopathic pulmonary artery hypertension (PAH) that RV global longitudinal strain may be a more sensitive parameter to detect early RV dysfunction and may be better at predicting outcomes [18•]. They demonstrated that if the RV strain does not improve over

time after treatment, these patients have worse outcomes [18•]. Interestingly, similar to RV strain, TAPSE was worse in non-survivors but the difference in TAPSE over time between the survivors and non-survivors was not as divergent as between RV strain in a 5-year follow-up [18•]. RV strain can also be derived from 3D echocardiography acquisitions with the post-processing software demonstrating RV longitudinal free-wall and septal strain (Fig. 1b) [14•, 34]. Vitarelli et al. demonstrated that in chronic PH, both 2D and 3D strain parameters were better associated with RV failure hemodynamics than conventional echocardiographic indices [34]. In our pediatric PH patients, RV longitudinal free-wall strain was prognostic of adverse clinical outcomes [14•].

Right atrial (RA) mechanics can also be studied with speckle tracking echocardiography. The components of RA function can be studied and provide insight into RV diastolic function. There are three components to RA function: reservoir, conduit, and pump function (Fig. 1c). The reservoir function is maximal atrial filling, the conduit function is passive emptying of the RA to the RV, and the pump function is the active RA emptying into the RV also known as atrial kick [35•]. Interaction of RA-RV strain can be studied and are interrelated. Mendes et al. demonstrated that in normal patients with normal RV strain where there is high ventricular deformation, there is high atrial deformation as the RV pulls down on the RA [36]. With low RV deformation, there is low atrial strain [36]. Querejeta Roca et al. studied RA function in patients with PAH and found that RA reservoir and passive conduit functions are impaired in PAH, independent of RA size and pressure, and likely reflect RV failure and overload [37•]. In adult studies of 108 idiopathic PAH patient, D'Alto et al. demonstrated that patients with worse reservoir function have worse prognosis [38]. In our study with 66 pediatric PH patients compared to 36 normal controls, all phases of the RA function were depressed in PH patients and that RA reservoir, pump function, and minimum volumes were predictors of adverse clinical events [16•]. This study highlights the difference between pathophysiologic difference between adults and children [16•]. In adults, the pump function is more affected at the time of the diagnosis but it is more preserved in children. This preservation of atrial contractile function is important in maintaining RV filling as the RV gets stiffer and less compliant through disease progression. Similar pediatric study showed that the active right atrial emptying fraction predicts reduced survival in PAH patients [39•]. Assessment of atrial size and function may allow for

assessment of RV diastolic function as traditional echocardiographic indices for RV diastolic function in pediatrics are still poorly validated [40]. RA function also allows for understanding of RA-RV interactions in pediatric PH; however, RA function cannot be used in the setting atrial level shunts or significant tricuspid regurgitation. Currently, RA function needs to be standardized as the tools of speckle tracking to evaluate RA function are taken from left atrial strain and normal pediatric values are still lacking.

Right ventricular pulmonary arterial coupling

The relationship between RV contractility and RV afterload is often referred to as RV-PA coupling. The main cause of mortality in PH is right ventricular (RV) failure with inability of the RV to maintain cardiac output with increasing arterial afterload, thus decoupling of the ventricular-pulmonary circulatory system [41••, 42]. From invasive pressure-volume loop analysis, the most widely accepted index of RV-PA coupling uses the ratio between ventricular elastance (E_{es} ; a measure of contractility) to arterial elastance (E_a ; a measure of afterload) [43••, 44]. The optimal RV-PA coupling allows for flow ejection at a minimal energy cost and corresponds to an E_{es}/E_a ratio of 1.5 to 2.0 [43••]. In patients with PH, the RV adapts to the increase in pulmonary arterial afterload by increasing E_{es} to preserve E_{es}/E_a [45]. Surrogates of E_{es}/E_a ratio using noninvasive methods such as the ratio between RV systolic pulmonary artery pressure (sPAP) and RV end-systolic area, TAPSE/sPAP, or RV strain/sPAP have been proposed [46, 47, 48•, 49]. Guazzi et al. demonstrated that the ratio of TAPSE/sPAP correlates with invasive coupling index of E_{es}/E_a and with compliance, representing an independent predictor of worse outcome in heart failure with preserved EF [50]. However, this TAPSE/sPAP is difficult to use in children because the noninvasive estimation of sPAP is based on

Doppler velocity of tricuspid regurgitation by Bernoulli's equation, an approach in pediatric patients that may at times imprecisely correlate with cardiac catheterization pressures [51]. Others have proposed using pulmonary acceleration time (PAAT) to replace sPAP in the TAPSE/sPAP ratio as PAAT has been demonstrated as a reliable estimate of invasive PAP in the absence of reliable tricuspid regurgitation [52•]. The ratio of TAPSE/PAAT as a surrogate of E_{es}/E_a warrants future investigation in children [53].

Another estimate of RV-PA coupling ratio is the non-invasive volumetric estimate proposed by Sanz [54•]. In this method, the coupling ratio is further simplified for pressure and expressed as stroke volume (SV)/end-systolic volume (ESV) (Fig. 1d) [54•]. This SV/ESV derived from CMRI has been demonstrated in adults with PH as an independent predictor of outcome and has been shown to be more sensitive than RV EF to changes in function early in the disease [55]. In 17 pediatric PH patients, Truong et al. demonstrated the feasibility of SV/ESV ratio from CMRI and found correlation to cardiac catheterization evaluation of the RV-PA coupling ratio using the single beat method [56•]. The volumetric estimate of the RV-PA coupling using SV/ESV ratio can be derived from 3D echocardiography as 3D echocardiography is readily available and more cost effective. This SV/ESV ratio has been shown in adults with PH to correlate with right heart catheterization-CMRI-derived RV-PA coupling ratio [57•]. Their study suggests further evaluation of outcomes using this volumetric estimate of RV-PA coupling ratio in the future [57•]. We have embarked on the study using SV/ESV derived from 3D echocardiography to evaluate pediatric PH patients compared to controls and have found a prognostic value of this SV/ESV ratio to adverse clinical events [58].

Conclusion

The advanced imaging tools available to evaluated pediatric PH patients provide insight into the RA-RV axis and the RV-PA coupling. 3D echocardiography provides volumetric and functional assessment that allows for quantitative assessment of the right heart without geometric assumptions. Myocardial mechanics using speckle tracking imaging provide assessment of the RA and RV function and provide further insights into the diastolic function of the right heart that have been poorly understood in the pediatric PH patients. Lastly, the

RV-PA coupling ratio further illustrates the interaction of the RV to the vasculature in the pulmonary circulatory unit. These advances are crucial in delineating the outcomes in pediatric PH patients and to the understanding of the RV to pulmonary unit in children with PH.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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