Diagnostic Challenges in Pediatric Pulmonary Hypertension

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As with any rare disease, a low prevalence in the population is a setup for missed diagnosis. Pulmonary hypertension (PH) can occur at any age during childhood and like in adults, a delay in diagnosis is common.[1] Historical outcomes for idiopathic pulmonary arterial hypertension are worse than adults, with a mean survival of 10 months after diagnosis.[2] This highlights the need for accurate workup for a potential pediatric PH diagnosis. Generally the evaluation process has paralleled the adult guidelines.[3,4] However, adult guidelines lack evidence-based support in pediatrics.[5] Recently the American Heart Association and American Thoracic Society created guidelines for the diagnosis and management of pediatric PH.[6] The guidelines offer a diagnostic algorithm needed to verify the diagnosis and work up potential etiologies (Figure 1). They provide the best evidence-based support for the workup and rationale involved. However, the guidelines are still hindered in that the majority of the evidence to support them is Level B (data derived from limited populations)[6] (Table 1). This review will discuss some of the diagnostic challenges in pediatric PH.

SUSPICION OF PULMONARY HYPERTENSION

Having a suspicion of pulmonary hypertension (PH) is difficult as symptoms can be nonspecific and differ by age of the patient. The main symptoms of PH are dyspnea on exertion and fatigue in adults[4] and children.[7] During this initial assessment, a patient's functional status is determined as scored by the World Health Organization (WHO).[4] This I to IV scale of worsening symptoms and activity tolerance is used in the adult population and has been applied to pediatrics with some predictability in PH outcomes.[8] However, with infants and young children, this assessment doesn't work well to describe their functional status. Therefore, a pediatric-specific classification divided by age group has been proposed (Table 2).[9] This format has advantages in its applicability to children, but has not yet been fully validated.[8] Additional findings from physical examination such as loud S2, tricuspid or pulmonary regurgitation murmurs, and hepatomegaly are supportive of possible PH, but their absence doesn't rule out PH.

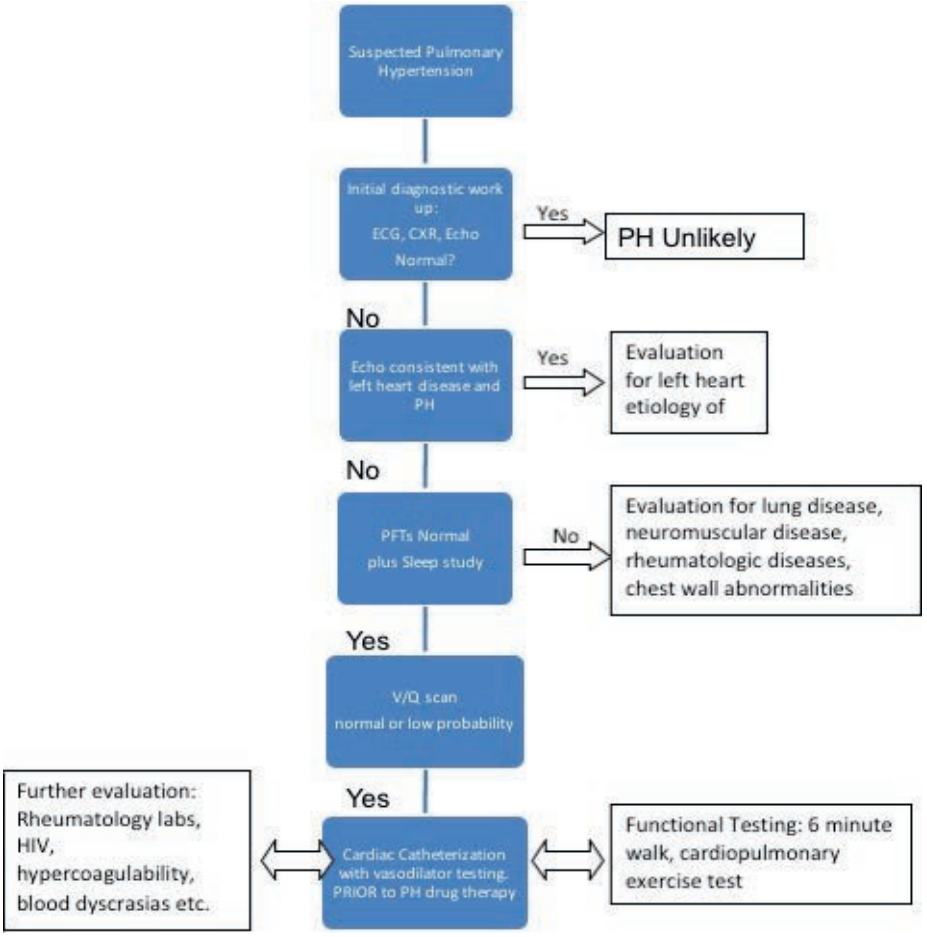

Figure 1: Diagnostic flow diagram based on AHA/ATS pediatric guidelines.[6] V/Q=ventilation/perfusion; PFT=pulmonary function test.

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Table 1. Class I Recommendations and Levels of Evidence (LOE).[6]

At initial diagnosis, a comprehensive history and physical examination combined with diagnostic testing for the assessment of PH pathogenesis/classification and formal assessment of cardiac function should be performed before the initiation of therapy at an experienced center.	Class I; LOE B
After a comprehensive initial evaluation, serial echocardiograms should be performed. More frequent echocardiograms are recommended in the setting of changes in therapy or clinical condition.	Class I; LOE B
Imaging to diagnose pulmonary thromboembolic disease, peripheral pulmonary artery stenosis, pulmonary vein stenosis, pulmonary veno-occlusive disease, and parenchymal lung disease should be performed at the time of diagnosis.	Class I; LOE B
A sleep study is recommended as part of the diagnostic evaluation in patients at risk for sleep-disordered breathing and in patients with PH and poor responsiveness to PAH-targeted therapies.	Class I; LOE B
Cardiac catheterization is recommended before initiation of PAH-targeted therapy (exception in critically ill patients requiring immediate initiation of empirical therapy).	Class I; LOE B
Cardiac catheterization should include AVT unless there is a contraindication.	Class I; LOE A
Minimal hemodynamic change that defines a positive response to AVT for children should be considered as a ≥20% decrease in mPAP and no change or increase in CO and decrease or no change in PVR/SVR.	Class I; LOE B
Repeat cardiac catheterization is recommended 3 to 12 months after initiation of therapy to evaluate response or clinical worsening.	Class I; LOE B
Serial cardiac catheterizations with AVT are recommended during follow-up with intervals based on clinical judgment but including clinical worsening or failure to improve during treatment.	Class I; LOE B
6MWD test should be used to follow exercise tolerance in pediatric PH patients of appropriate age.	Class I; LOE A
BNP or NT-proBNP should be measured at diagnosis and during follow-up to supplement clinical decisions.	Class I; LOE B

AVT=acute vasoreactivity testing; CO=cardiac output; PVR/SVR=pulmonary vascular resistance/systemic vascular resistance; 6MWD=6-minute walk distance.

INITIAL NONINVASIVE TESTING/ ECHOCARDIOGRAPHY

According to the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry, electrocardiogram, chest x-ray (Figure 2), and echocardiogram (echo) were the most frequent tests performed, and at least one was abnormal out of 456 patients reviewed.[5] Echocardiography is the primary noninvasive test to evaluate and follow PH (Figure 3). It serves multiple roles, including identification of congenital heart disease, estimation of pulmonary artery pressures (PAPs), pulmonary vascular resistance (PVR), and right ventricular (RV) size and function.[10] In the TOPP registry, echo was reported as abnormal 99% of the time it was used in catheterization-confirmed PH cases.[5]

Use of the tricuspid regurgitation (TR) gradient is the primary way to estimate pulmonary artery systolic pressure through the modified Bernoulli equation (pressure = 4 times TR velocity^2), as long as there is no obstruction across the RV outflow tract.[11] There are several challenges using TR gradient to estimate PAP. The first is the availability of a reliable TR gradient, which may be inadequate in up to 25% of patients.[6] It depends on the best peak TR velocity obtainable, and too little or too much TR present can lead to underestimation of catheterization-derived pressures.[11] In addition, very high PAPs may have their pressures overestimated when using echo.[12] Echo measurements in adults do have a very good accuracy across populations when comparing PAPs, left atrial pressures, and PVR to catheterization data, but these measurements lack precision.[13] This creates a wide range of upper and lower limits in the confidence intervals, thus limiting their use in individual clinical manage-

Table 2. Generalized Pediatric Functional Classification Scale for Ages Newborn to 16 Years.[9]

Class I	Class II	Class IIIa	Class IIIb	Class IV
Asymptomatic, growing and developing normally. No physical limitations	Slight limitation in physical activity. Dyspnea with playing. Normal growth. If in school, 75% attendance rate	Marked limitation in physical activity. Comfortable at rest. If in school, <50% attendance	Growth severely compromised, poor appetite. If walking age, wheelchair needed outside home. Unable to attend school. Plus IIIa findings	Unable to do physical activity. Unable to interact with family. Syncope or right heart failure. Plus III findings

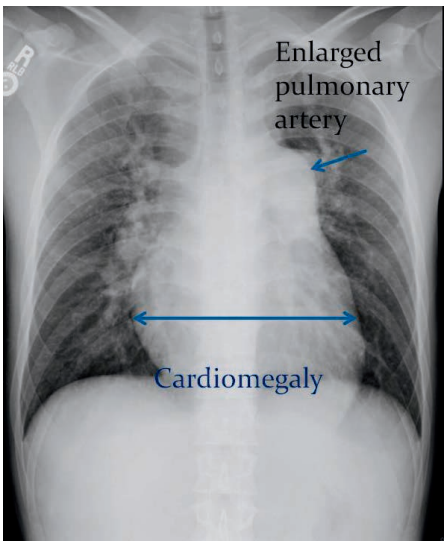

Figure 2: Chest x-ray of a patient with PH. Findings include evidence of cardiomegaly and enlarged main pulmonary artery.

ment.[13] A meta-analysis of 2600 echo Doppler and right heart catheterization (RHC) correlations has shown that right heart–related disease (eg, idiopathic PH) leads to only a moderate correlation (r=0.58±0.14) with RHC PAPs.[14] This study also found an echo Doppler–RHC PAP difference >10 mm Hg in 37.6±13.1%.[14] In pediatrics, clinical use of echo to estimate PAPs uses the same approach as in adults.[10] Using TR gradient >40 mm Hg to signify PH, echo Doppler in small children showed an 88% sensitivity and 33% specificity to RHC evidence of PH.[15] These values improved when the additional findings of septal flattening, RV hypertrophy, and dilation were also present to a sensitivity of 94% and specificity of 67%.[15] It has been recommended to use estimated right atrial pressure (RAP) when trying to quantify the RV pressure with echo.[6] However, a pediatric/young adult study found calculated right atrial volume measurements had only modest correlation with RAP (r=0.51, *P*>0.001) and no correlation with inferior vena cava collapsibility index.[16] Caution is needed with estimation of RAP, as it can lead to inaccuracies of PAP estimate by echo Doppler.[12,15]

Functional assessment of the RV is very important, as RV function is more predictive of survival in PH than PVR.[17] Use of visual estimation of RV function and size is common practice, but its correlation with objective assessment such as magnetic resonance imaging is inaccurate and quite variable.[18] Use of objective measures such as tricuspid annular planar systolic excursion measurement has good correlation with RV function[18] in adults, and some evidence has been found to correlate with survival in pediatrics.[19] As a whole, these findings demonstrate the utility and limitations of echo in pediatrics. Echo works well for initial assessment of PH etiology and for serial follow-up, but lacks individual specificity to solely diagnose PH and document its severity well enough to initiate treatment in most settings.

PULMONARY FUNCTION AND OXYGENATION TESTING

Evaluation for lung disease is part of the workup for PH. This includes the use of chest x-rays, pulmonary function testing (PFT), and at times chest computerized tomography (CT). The use of PFTs can be limited by the patient's age and/or level of maturity to cooperate with the test. Studies have shown that children as young as 3 years can successfully perform PFTs.[20] In addition, evaluation for hypoxia is important as nocturnal hypoxia can be commonly seen in idiopathic pulmonary arterial hypertension (IPAH) patients and may not be due to apnea alone.[21] Intermittent hypoxia has been shown to perpetuate pulmonary arterial hypertension with improvement in PAP seen after interventions to prevent hypoxia such as continuous positive airway pressure for treatment of obstructive sleep apnea (OSA).[22,23] In pediatrics abnormal pulse oximetry has been used to predict the presence of OSA, though a normal test does not rule it out.[24] Surgical adenotonsillectomy has been shown to improve OSA in 90% of pediatrics patients, though most will still have some residual disease.[25] Identification of lung disease and intermittent hypoxia can lead to potential therapies that may improve PH.

EVALUATION FOR PULMONARY EMBOLISM

Pulmonary embolism (PE) is more readily recognized in the adult population as it is the third most common cause of cardiovascular disease.[26] In pediatrics, PE is much less common with an incidence of 0.14 to 0.49 per 10,000

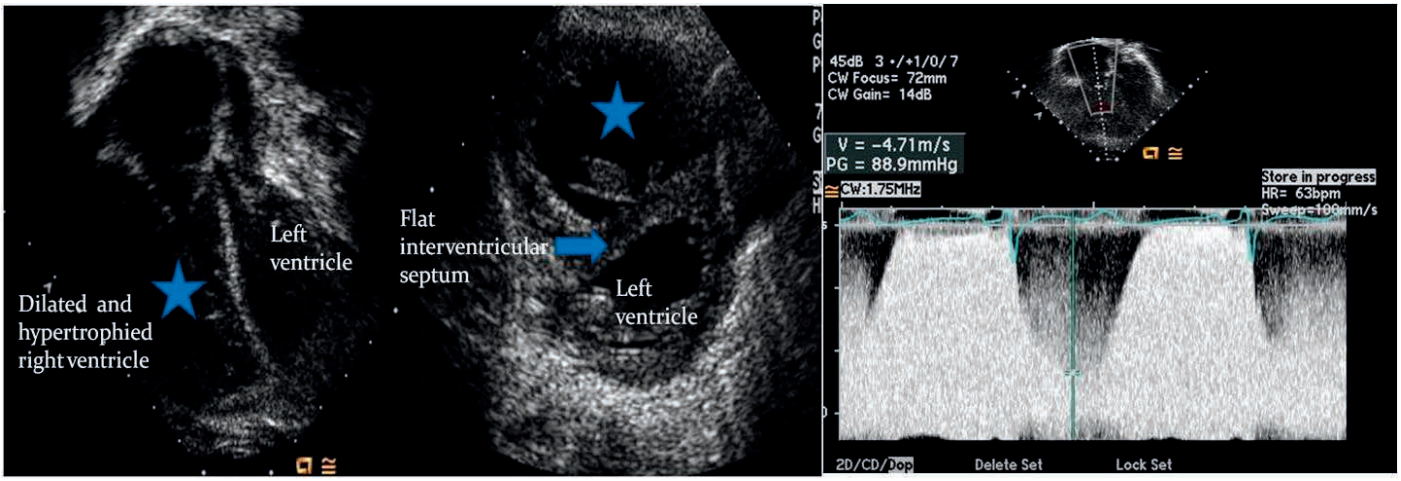

Figure 3: Echocardiogram of a child with severe PH. Dilated and hypertrophied right ventricle and flattened interventricular septum can be seen. The measured tricuspid regurgitation gradient is markedly elevated at 89 mm Hg.

children per year,[27,28] and is mainly found in sick neonates and adolescents.[27] The adult algorithm for PH workup includes the need to evaluate for chronic PE.[3] However, the TOPP registry notes <1% of pediatric PH cases were due to chronic PE (Group 4).[5] There are no suitable studies to determine the predictive value of diagnostic tests for PE in pediatrics.[27] The 2015 American Heart Association (AHA) guidelines discuss the use of ventilation/perfusion (V/Q) scan or CT angiography to assess pulmonary blood flow and obstruction.[6] Outside of pulmonary angiography as the "gold standard," a V/Q scan has been the traditional noninvasive means to evaluate for PE in adults, but those guidelines have not been well established in children.[26] The low-dose radiation risk in the absence of suspected lung disease would be an indication for this modality to be used first.[27] A normal perfusion scan is reassuring for no PE,[27] but V/Q scans can be unreliable in congenital heart disease (especially right-to-left shunts) and pulmonary artery stenosis lesions.[26] A helical pulmonary angiography CT is able to see pulmonary artery branches to the sixth segmental division with a 60% to 100% sensitivity and 81% to 100% specificity in adults for identifying a PE.[27] In addition, a CT can identify pulmonary parenchymal disease, making this the modality of choice.[28] However, there are real concerns over radiation exposure and future cancer risk in pediatrics with CT scanning.[27] Newer protocols using dual-energy CT angiography with reconstruction algorithms can lower radiation exposures.[28]

CARDIAC CATHETERIZATION

Cardiac catheterization is the "gold standard" in hemodynamic assessment and is important in diagnosis and treatment of PH in order to: 1) confirm the presence of PH; 2) make the distinction between right heart– vs left heart–related disease; 3) measurement of PVR; 4) calculation of shunts; 5) delineation of extracardiac anatomy and pressure gradients; 6) vasoreactivity testing to stratify patient treatment.[6]

There are several challenges involving the use of cardiac catheterization in pediatric PH. One key difference from adult management is the routine use of general anesthesia in young children when performing a cardiac catheterization. The need for intubation and mechanical ventilation can affect hemodynamics in PH patients if respiratory acidosis from hypoventilation were to develop, which can worsen PVR.[29] The use of volatile anesthetic gases can lower PAPs and cardiac index, which will affect the validity of the data.[29] When measuring cardiac output in patients, especially those with shunts, the use of the Fick principle (cardiac output = oxygen uptake [VO_2]/arterial-venous oxygen difference) is the standard to calculate hemodynamic measures.[30] This requires knowledge of the VO_2 level for the patient, which is commonly estimated through predictive equations instead of direct measurement.[30,31] In adults, estimation of VO_2 has been found inaccurate, especially with obese patients.[32] In pediatric congenital heart disease patients, estimations of VO_2 have also been found inaccurate when compared to direct VO_2 measurement.[30] Pediatric patients with structurally normal hearts have been shown to have good agreement between thermodilution-calculated cardiac output and direct measurement of VO_2 with the use of the Fick equation to calculate cardiac output.[31] Estimation of VO_2 by the LaFarge and Lundell equations have also been found to have fair agreement with direct measurement values, though the LaFarge method of calculation yields significantly lower VO_2 than direct measurement.[31]

One of the most concerning aspects of pediatric catheterization is the occurrence of complications. The event rate of any complication (ie, death, vascular injury, arrhythmia, bleeding) has been found to be around 7.3%.[33] Age <6 months was associated with more major complications including death (odds ratio 4.4 [1.88-10.35]).[33] When reviewing inpatient children and young adults with PH undergoing a cardiac catheterization, the incidence of death or need for extracorporeal membrane oxygenation (ECMO) was 3.5%.[34] Premature infants had the highest risk with an odds ratio of 4.95 (1.3-18.86).[34] Death alone had a 0.3% incidence,[34] which is much higher than the adult PH patient-reported incidence of 0.05%.[35] Cardiac catheterization is an essential part of the diagnosis and management of PH, but it has unique caveats and potential risks when used in the PH pediatric population and should only be performed in experienced pediatric centers.

EXERCISE TESTING

Objective functional testing is important during the initial evaluation and follow-up in PH. Results of cardiopulmonary exercise testing (CPET) have correlated with cardiac output and overall mortality in cardiomyopathy.[36] In pediatric PH, CPET has shown good correlation with PVR index, WHO functional class, and moderate correlation with PAP.[37] In addition, CPET can help identify exercise intolerance, arrhythmias, and desaturation with exercise.[38] CPET is limited in pediatrics in that a child needs to be capable and mature enough to perform the test, which is usually around 7 years of age.[38] The 6-minute walk test (6MWT) has the advantage of being a submaximal exercise test, which is important in patients who are not able to ambulate well or lack the maturity for CPET.[36] The 6MWT has been found to correlate with functional class and survival in adults.[36] In addition, each 1% decrease in saturation during a 6MWT has also been found to have a hazard ratio of 1.26 (1.04-1.26) for death in PH adult patients.[39] A 6MWT can be performed even in small children with good correlation to CPET-calculated oxygen consumption up to 300 meters, but then loses this correlation at longer distances.[40] This may encourage using CPET in more able-bodied children.

LABORATORY ASSESSMENT

During the diagnostic workup for PH, laboratory data are used to narrow the differential of potential etiologies. This includes evaluation for connective tissue disease, infections, liver disease, and blood dyscrasias.[6] Biomarkers of ventricular overload such as B-type natriuretic peptide (BNP) have a high sensitivity (87% to 97%) for cardiac disease including PH in children.[41] However, BNP levels can be falsely

elevated with sepsis, renal disease, and stroke.[42] Clinically there has been found to be a positive correlation with worsening WHO functional status and elevated BNP levels in pediatric PH patients.[43] Serial BNP levels can demonstrate change over time that better relates to changes in hemodynamic status in pediatrics.[44] BNP has become a useful marker for following pediatric PH.

CONCLUSION

The new pediatric guidelines are a welcome resource for pediatric PH providers. These guidelines provide a unique pediatric-focused blueprint in the diagnostic workup for PH to confirm the diagnosis while searching for potential etiologies that will aid in treatment. This workup should risk-stratify these patients, which will determine their initial therapies. Like all guidelines, they need to be used with the individual patient in mind. Test choices, testing order, and use of other tests not mentioned should be decided by a case-by-case basis. Experience is still needed to overcome limitations and unresolved issues with pediatric PH evaluation. This further highlights the importance of centers of excellence that have such experience.

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