REGULAR ARTICLE

Pediatric Pulmonary Hypertension in Left-Sided Heart Disease

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Pulmonary hypertension (PH) from left-sided heart disease (group-II PH) is an increasingly recognized cause of PH in pediatrics. Group-II PH can result from obstruction at any level of the left heart, and can progress over time. Management can be particularly difficult, as targeted PH therapy in the setting of a fixed obstruction carries a risk of pulmonary vascular congestion and pulmonary edema. Based on existing evidence, the use of pulmonary vasodilators in group II PH is not recommended, and management centers around early identification and correction of the underlying left-sided lesion. In this review, we highlight the pathophysiology of group-II PH, the diagnostic evaluation of left heart pathology, and a general approach to both medical and surgical management, with particular attention to relevant left-sided lesions. Group-II PH is a multifaceted and progressive disease process that poses a difficult challenge to clinicians, and requires a thoughtful and individualized approach to management.

INTRODUCTION

Pulmonary hypertension (PH) is a rare disease in children and is associated with significant morbidity and mortality.[1] Data from various registries have shown that 6th World Symposium of Pulmonary Hypertension (WSPH) group I and group III are the commonest forms; however, group II PH in pediatric patients has achieved increasing recognition in the two more recent WSPH classifications of PH.[2,3] PH from left-sided heart disease (group II PH) results when left heart pathology transmits passive hydrostatic pressure to the pulmonary vascular tree, first to the post–alveolar-capillary pulmonary venous system and then to the pre–alveolar-capillary pulmonary arterial system.[4,5]

Although epidemiologic data in pediatric patients are limited, group II PH is becoming increasingly common, accounting for 5% to 14% of cases of pediatric PH.[2,5,6] While left ventricular (LV) systolic dysfunction is the primary cause of PH in adults, pediatric group II PH can be secondary to obstruction at any level of the left heart, including pathology of the pulmonary veins or the mitral or left atrioventricular valve (LAVV), LV systolic or diastolic dysfunction, or LV outflow tract obstruction.[7,8] These lesions can occur in isolation or in combination with each other, such as in Shone complex, and can progress and worsen over time.[9]

Group II PH can be further subdivided into two categories: postcapillary PH and combined precapillary and postcapillary PH (Cpc-PH).[8] Elevations in left-sided pressures lead to distension and endothelial disruption of the post–alveolar-capillary vasculature, resulting in remodeling, including smooth muscle proliferation and intimal and medial thickening.[8] The pulmonary veins, which normally lack a significant muscular medial layer, develop histologic features resembling pulmonary arterioles. This vascular remodeling helps mitigate the backward transmission of elevated left-sided pressures, at the expense of increased resistance to the left atrium (LA) leading to increased mean pulmonary artery (mPA) pressure and so-called postcapillary PH. Cpc-PH occurs with chronic elevations in left-sided pressures, which, if not adequately addressed, results in the remodeling of the pulmonary arterial system, including hypertrophy, fibrosis, thrombosis, and an increase in resistance in the pulmonary vasculature.[10]

Both isolated group II PH and Cpc-PH share common hemodynamic definitions reflective of the underlying pathophysiology, including mPA pressure of ≥20 mm Hg and pulmonary capillary wedge pressure (PCWP) of ≥15 mm Hg. Cpc-PH is further differentiated from isolated postcapillary PH by hemodynamic measurements reflective of increased pulmonary vascular resistance, either a transpulmonary gradient (TPG) of ≥7 mm Hg or an indexed pulmonary vascular resistance (PVRi) of ≥3 Wood units · m^2 (WU m^2).[2] Given the high prevalence of group II PH in adult populations, the most recent European Society of Cardiology/Respiratory Society adult guidelines have lowered the threshold for the diagnosis of Cpc-PH to a PVR of >2 WU; however, these criteria have not yet been adopted for pediatric populations.[11]

GENERAL APPROACH

Evaluation and management of group II PH are largely dependent on the underlying etiology of left heart disease, and much of the current understanding of this physiology comes from experience in adult populations with left heart failure and either a preserved or reduced ejection fraction. The use of pulmonary vasodilators in adult as well as pediatric

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Table 1. Echocardiographic Parameters and Measurements Included as Part of the Evaluation of Pediatric Group II Pulmonary Hypertension

Echocardiographic Evaluation of Pediatric Group II Pulmonary Hypertension	
Right-Sided Chamber Dimensions	**Mitral Valve or LAVV**
Right atrial size	2D and color Doppler assessment of LAVV
Right ventricular end-diastolic volume	Pulsed-wave Doppler assessment
Right ventricular hypertrophy	Continuous-wave Doppler assessment
	Mean gradient measurement of LAVV inflow
Right Ventricular and Pulmonary Artery Pressure	**Left Ventricular Diastolic Function**
Tricuspid regurgitation jet	Lateral LAVV annulus tissue Doppler assessment
Interventricular septum position	LV inflow Doppler measurements
Pulmonary regurgitation gradient (peak and end diastolic)	
Right Ventricular Function	**Left Ventricular Systolic Function**
Qualitative systolic function assessment	Qualitative systolic function assessment
TAPSE	Quantitative systolic function assessment
Right ventricular FAC	Left ventricular strain measurement
Right ventricular MPI	Left ventricular dp/dt measurement
Right ventricular strain measurement	
Pulmonary Veins	**Aortic Valve and Aorta**
2D and color Doppler assessment of all 4 pulmonary veins	2D and color Doppler assessment of aortic valve
Mean gradient measurements	2D and color Doppler assessment of ascending and transverse aorta and aortic isthmus
	Pulsed-wave Doppler assessment of descending aorta

Abbreviations: FAC indicates fractional area change; LAVV, left atrioventricular valve; LV, left ventricular; MPI, myocardial performance index; TAPSE, tricuspid annular plane systolic excursion.

group II PH varies by center without a single unifying strategy, and treatment is considered off-label due to the lack of supporting data. Central to the management of pediatric group II PH is the timely identification and surveillance of the underlying lesion and the reduction of the hydrostatic pressure in the alveolar capillary bed while monitoring for signs of worsening pulmonary edema.

Diagnostic Evaluation

The diagnostic evaluation of a patient with group II PH has to account for the many underlying etiologies.[12] A thorough history should include evidence of effort intolerance, fatigue, respiratory distress, and failure to thrive as well as prior diagnoses of congenital heart disease or myocarditis/cardiomyopathy. Physical examination findings can be useful to localize left-sided lesions, such as an opening snap and diastolic murmur in mitral or LAVV stenosis, a gallop in LV systolic or diastolic dysfunction, or diminished femoral pulses with brachiofemoral delay in coarctation of the aorta.

Laboratory testing, including B-type natriuretic peptide (BNP) or N-terminal ProBNP (NTProBNP), has been used in the surveillance of PH in both adults and children.[13] Serial NTProBNP measurements may reflect left atrial distension and the progression of group II PH.[14] Chest radiography may demonstrate cardiomegaly consistent with the disease or reveal evidence of pulmonary vascular congestion. Chest radiographs in this population are less likely to show significant oligemia as can be seen in other types of PH as the PH is secondary to vascular congestion.

An electrocardiogram (ECG) is a noninvasive tool to assess for structural heart disease of the left heart. ECG may demonstrate evidence of left heart dilation or hypertrophy, left-axis deviation, or left atrial enlargement. ECG can also help identify atrial arrhythmias, which can occur in LA dilation secondary to left-sided obstructive disease.

Echocardiography

Echocardiography can be pivotal in the diagnosis of group II PH. A complete and thorough anatomic assessment is essential to evaluate all lesions contributing to group II PH.[2,3,12] Echocardiographic assessment, including color Doppler, can be used to evaluate for LAVV stenosis or regurgitation, aortic stenosis (AS), aortic hypoplasia, or coarctation of aorta (CoA). Each echocardiogram for a patient with concern for PH should include a thorough evaluation of all four pulmonary veins as pulmonary vein stenosis (PVS) has a variable onset and can be progressive. Qualitative and quantitative function assessments, including LV strain measurements, are necessary to evaluate for LV systolic dysfunction. Diastolic function may be difficult to fully assess using echocardiography but can be supported by abnormalities of left atrial size, tissue Doppler velocity of the LAVV lateral annulus, and/or pulsed-wave Doppler profile of the LAVV inflow.[15]

Echocardiography can provide an estimate of right ventricular (RV) and pulmonary artery pressure with a combination of the interventricular septal position, tricuspid regurgitation jet, and pulmonary regurgitation jet, as well as evaluating for RV systolic dysfunction.[3] A comprehensive list of echocardiographic parameters as part of group II PH assessment is included in Table 1.

Cardiac Catheterization

Cardiac catheterization allows for direct measurements of mPA pressure as well as PCWP. Additionally, actual measurements of the TPG and the PVR can be useful in differentiating isolated postcapillary PH (TPG, <7 mm Hg; PVRi, <3 WU m^2) from Cpc-PH (TPG, ≥7 mm Hg; PVRi, ≥3 WU m^2).[3,16]

If there is concern for group II PH, additional measurements in the left heart can be taken to diagnose the underlying pathology, stratify severity, inform surgical decision-making, and, in some cases, even provide interventions to relieve left-sided obstruction. This can be particularly useful in group II PH secondary to more than one form of left-sided obstruction. A complete hemodynamic assessment must include measurements of pressure gradients along the left heart, including the pulmonary veins and the LAVV, or across the LV outflow tract. Measurement of the LV end-diastolic pressure can be useful in determining diastolic dysfunction that may be either contributory to or the underlying cause of PH.[8,9]

Acute vasodilator testing with inhaled nitric oxide should be done very carefully (with watch for the development of pulmonary edema) and may provide anticipatory guidance prior to the use of pulmonary vasodilators by documenting any change in right heart hemodynamics, including a reduction in the mPA pressure or PVR, but, more importantly, monitoring for a corresponding increase in the PCWP.[3,16] Great care is needed if vasoresponsiveness testing is done as increasing pulmonary blood flow could lead to pulmonary edema in patients with group II PH.

Pulmonary Vasodilator Therapy

While pulmonary vasodilator therapy is a mainstay of precapillary PH, its use in pediatric group II PH is risky.[17] Vasodilation of the pulmonary vasculature in the setting of left-sided obstructive disease can worsen pulmonary vascular congestion and lead to pulmonary edema. Even after medical or surgical correction of left-sided disease, the remodeling of the postalveolar capillary vessels takes time to normalize, and the initiation of pulmonary vasodilators can still have deleterious effects.

Most of the current data regarding medications in group II PH come from adult trials investigating medical therapies, and there is a significant need for similar research in pediatric populations. The phosphodiesterase-5 inhibitor sildenafil is the most-studied drug in group II PH. An early randomized, placebo-controlled study of sildenafil in adult patients with heart failure showed improvements in functional status in those taking sildenafil as well as improvements in echocardiographic indices of LV diastolic function.[18] However, subsequent trials in adults with heart failure and valvular heart disease have failed to show a benefit, even suggesting potential harm.[19,20] Similar trials in adults with heart failure investigating the use of endothelin receptor antagonists have shown no significant benefit, with increased fluid retention and worsening symptomatology in treatment groups.[21] A randomized, placebo-controlled trial of epoprostenol in adults with heart failure was stopped prematurely due to increased mortality observed in the treatment arm.[22] Based on existing evidence, the use of pulmonary vasodilators in group II PH is not currently recommended for adult or pediatric patients.[11] Patients with Cpc-PH and a PVRi elevated out of proportion to their left-sided obstructive disease present a challenge to pediatric practitioners, and currently, no consensus practice exists regarding the use of pulmonary vasodilators in these patients. Most pediatric pulmonary hypertension specialists may choose to use small doses of pulmonary vasodilators very carefully, along with diuretics, in patients with evidence of Cpc-PH on cardiac catheterization and clinical evidence of response to some pulmonary vasodilation.[6] When utilized, vasodilator therapy is initiated cautiously, often with a phosphodiesterase-5 inhibitor and less commonly with an endothelin receptor antagonist. Due to the risk of pulmonary edema and evidence of harm from adult trials, prostaglandin-based therapies are not used in group II PH.

Other Medical Therapies

Medical therapy in children with group II PH should focus on minimizing pulmonary vascular congestion and promoting flow into and out of the left heart to minimize the hydrostatic pressure on the post–alveolar-capillary venous system. Diuretic therapy can help relieve pulmonary vascular congestion in group II PH, improving symptoms and slowing progression to precapillary PH. Rate control with either a beta blocker or digoxin can encourage diastolic filling time, decompressing the LA in the setting of LAVV stenosis or LV diastolic dysfunction with LV afterload reduction. LV dysfunction can also be medically treated with digoxin, angiotensin-converting enzyme (ACE) inhibitors, and diuretics, including spironolactone, and in cases of severe dysfunction, intravenous inotropes may be needed.[22]

PULMONARY VEIN STENOSIS

PVS is an emerging cause of both left-sided obstructive disease and PH with increased survival of infants born extremely preterm.[23] PVS can be either primary, affecting normally draining pulmonary veins, or secondary to anomalous pulmonary venous return that has been surgically repaired, with stenosis at the anastomosis site or in the distal veins. The underlying pathobiology of primary PVS is poorly understood and is likely multifactorial with known associations with prematurity and comorbid conditions, including bronchopulmonary dysplasia and necrotizing enterocolitis.[23,24]

Primary PVS is a heterogeneous disease characterized by neointimal proliferation at the area of stenosis. Disease can range from discrete stenosis at the venoatrial junction to diffuse hypoplasia of the extrapulmonary pulmonary

veins. PVS can involve one or more pulmonary veins and is often progressive, needing recurrent interventions, with high morbidity and mortality rates.[23–25] Due to its progressive nature, early identification using echocardiography is key. Computed tomography (CT) can be used to further evaluate the extent and location of vein stenosis or evidence of obliteration or atresia. Noninvasive imaging can underestimate pressure gradients, and cardiac catheterization is the gold standard for diagnosis. Catheterization can identify stenoses with angiography, directly measure pressure gradients, and allow for balloon angioplasty with or without stent placement.

Medications, including the mTOR inhibitor sirolimus, have been shown to slow the progression of the disease as well as improve rates of in-stent stenosis and neointimal proliferation.[26] Current surgical approaches for repair, including the so-called "sutureless repair," have led to improvements in rates of restenosis and mortality.[25] Current management strategies with frequent surveillance catheterizations and interventions every 6 to 8 weeks have improved long-term outcomes; however, mortality rates 5 years from diagnosis remain as high as 40%.[27]

COR TRIATRIATUM SINISTER

Cor triatriatum sinister is a rare congenital anomaly whereby an accessory membrane separates the LA into two chambers: a posterior chamber that receives blood flow from the pulmonary veins and an anterior chamber that drains across the LAVV into the LV. Restriction across this membrane prevents effective inflow into the LA and, if not addressed, can progress to group II PH. In severe cases, presentation can be early; however, in some cases, symptomatology can be vague, and diagnosis can be delayed well into adulthood.[28] Echocardiography is used to accurately make the diagnosis, and definitive treatment involves surgical resection of the intra-atrial membrane and is associated with favorable long-term outcomes with low rates of restenosis.

LEFT ATRIOVENTRICULAR VALVE OR MITRAL STENOSIS

Stenosis of the LAVV can occur in isolation or in combination with additional left-sided obstructive lesions, such as in Shone complex. LAVV stenosis can either be congenital or occur following repair of the LAVV.[29] These patients can develop group II PH with symptoms of pulmonary vascular congestion, hypoxia, or even syncope. Postrepair, there can be persistent PH, and overzealous vasodilator therapy may result in pulmonary vascular congestion and pulmonary edema.[30] Echocardiography can estimate mean pressure gradients across the LAVV, which can be further delineated by cardiac catheterization. Surgical repair by either valvuloplasty or valve replacement can have an effective result in lowering mPA pressure, with favorable outcomes.[31]

SHONE COMPLEX

Shone complex is a constellation of left-sided obstructive lesions, including LAVV stenosis with a supramitral ring, parachute LAVV, subaortic or aortic valve stenosis, and CoA. The extent and location of obstruction can be variable, and the degree of LAVV stenosis is one of the primary predictors of disease prognosis.[9] Compared to isolated congenital LAVV stenosis, the concomitant LV outflow tract obstruction seen in Shone complex, combined with a potentially hypoplastic or noncompliant LV, further exacerbates left-sided disease and increases the risk of group II PH. Additional reoperations and reinterventions also carry a risk of worsening diastolic dysfunction on what can often already be a dysfunctional LV. PH in Shone complex is a risk factor for reintervention and worsened outcomes.[32]

Repair is typically staged, with repairs of the aortic arch occurring earlier in infancy and delaying intervention on the LAVV until the patient reaches a favorable size for LAVV intervention. Close surveillance is needed to identify recurrent or worsening obstructive lesions and the development of atrial arrhythmias.

LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC DYSFUNCTION

LV dysfunction is the most common form of PH in adults and is becoming an increasingly recognized cause in pediatric patients.[3] LV dysfunction can be either systolic, diastolic, or a combination of the two. It can be secondary to dilated or restrictive cardiomyopathy or myocarditis, or it can occur following surgical repair of congenital heart disease.[2,3]

Echocardiography should be used for both qualitative and quantitative assessments of LV function. Careful assessment for reversible causes of LV dysfunction, such as coronary anomalies, should be performed. LV diastolic dysfunction leading to PH should be further evaluated using cardiac catheterization prior to therapy.[12,16] Catheterization allows for measurements of the PCWP and LV end-diastolic pressure and direct measurements of the cardiac index and PVRi. In patients with severe dysfunction requiring heart transplantation, a lowered PVRi following acute vasodilator testing can inform transplant candidacy and prognosis.[33]

Treatment of group II PH and LV dysfunction with pulmonary vasodilators has been studied in both animal models and adult clinical trials, but data are limited for pediatric patients. Sildenafil can promote LV remodeling in heart failure as well as improvements in LV systolic and diastolic performance.[34] Sildenafil has been associated with improvements in echocardiographic indices of PH in adults with LV dysfunction and is largely tolerated in pediatric patients when administered with careful, in-hospital titration.[35] Despite these findings, clinical trials show conflicting results for sildenafil with respect to its impact on clinical status, quality of life, or symptomatology.[18–20] The guanylate cyclase stimulator riociguat has also demonstrated improved hemodynamics in heart failure, without any difference in clinical symptoms.[36] Given the conflicting evidence and potential for harm, current guidelines recommend against the use of pulmonary vasodilator therapy in group II PH from LV dysfunction, and any use in pediatric populations is

considered off-label.[11] In patients with severe LV dysfunction, ventricular assist devices have been utilized to decompress the left heart, either as a bridge to heart transplantation or as destination therapy.[37]

AORTIC STENOSIS

AS is an uncommon cause of group II PH in children and is typically a late finding from decompensated heart failure. AS can be congenital, secondary to a bicuspid or even unicuspid aortic valve, or acquired secondary to rheumatic heart disease.[38] While clinically significant PH is uncommon, congenital AS is associated with remodeling and arterialization of the pulmonary venous vasculature, both in utero and in the early neonatal period.[3] This is likely due to changes in LV compliance in the setting of increased afterload, which can significantly improve following successful aortic valve intervention.[39] Balloon aortic valvuloplasty is often an initial transcatheter option for the treatment of congenital AS; however, in patients with more severe or long-standing disease, surgery with aortic valve repair or replacement is indicated.[38]

CONCLUSION

The management of group II PH can be extremely challenging due to the wide array of contributing left-sided lesions that lead to it. Management is directed toward correcting the left-sided lesions, treating volume overload with diuretics, and, in very select cases, targeted PH therapy. While the importance of reducing left-sided pressures and the underlying left-sided lesion is well known, an individualized approach is vital to appropriately manage each patient with group II PH.

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