Check for updates

Circulation: Heart Failure

AHA SCIENTIFIC STATEMENT

Clinical Management and Transplant Considerations in Pediatric Pulmonary Hypertension Due to Left Heart Disease: A Scientific Statement From the American Heart Association

Rachel K. Hopper, MD, Chair; Georg Hansmann, MD, PhD; Seth A. Hollander, MD; Anne I. Dipchand, MD; Oscar van der Have, MD; Colleen Iler, ACCNS-P; Cynthia Herrington, MD; Erika B. Rosenzweig, MD; Juan C. Alejos, MD; Karin Tran-Lundmark, MD, PhD, Vice Chair; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative & Resuscitation; Council on Clinical Cardiology; and Council on Cardiovascular Stroke Nursing

ABSTRACT: Children with left heart disease are at risk for developing pulmonary hypertension, initially secondary to pulmonary venous hypertension that can progress to include elevated pulmonary vascular resistance, known as combined pre- and postcapillary pulmonary hypertension. Elevated pulmonary vascular resistance may pose a risk to the right ventricle of a newly transplanted heart because of increased afterload and is an important consideration for heart transplant eligibility. However, the epidemiology, pathophysiology, optimal diagnostic and treatment approaches, and thresholds for pulmonary vascular resistance in pulmonary hypertension associated with left heart disease remain unclear because of lack of evidence, particularly in pediatrics. The result is heterogeneity with respect to hemodynamic assessment, use of pulmonary vasodilator therapies, and heart transplant listing. This scientific statement aims to synthesize the available data and highlight areas of general consensus as well as important knowledge gaps.

Circulation: Heart Failure

Key Words: AHA Scientific Statements ■ heart diseases ■ hypertension, pulmonary ■ pediatrics ■ transplantation

Downloaded from http://ahajournals.org by on December 10, 2024

In many countries, pediatric heart transplantation (HTx) is standard therapy for end-stage heart failure in children, which in most cases is caused by congenital heart disease or cardiomyopathy. Associated pulmonary hypertension (PH) can be an absolute or relative contraindication to HTx, depending on the level of elevation of pulmonary vascular resistance (PVR) and other clinical factors. Elevated PVR may deter centers from considering a child for HTx alone, raising the consideration of combined heart-lung transplantation, because of the risk of postoperative right heart failure from increased afterload to the right ventricle (RV) of the newly transplanted heart. However, long-term survival is significantly better with HTx compared with combined heart-lung transplantation; in addition, increased PVR secondary to left heart disease normalizes after transplant in most cases.[1]

Whereas assessment of PVR is part of the standard HTx evaluation in most centers, there is little consensus regarding PVR thresholds for HTx listing, particularly in children, largely because of lack of data. Recognition of the potential negative effect of elevated PVR on HTx outcomes and the goal to avoid lung transplantation have led to prevention and management strategies, including use of pulmonary vasodilator therapies. The evolution of ventricular assist devices (VADs) and their capacity to reduce left atrial (LA) and left ventricular (LV) end-diastolic pressure have also broadened the armamentarium of therapeutics used to treat PH in the pediatric HTx candidate. These strategies may also be used to treat persistent PH and RV dysfunction in the early post-HTx period, if needed. Clinical questions and management dilemmas encountered when assessing

© 2024 American Heart Association, Inc.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

children with elevated PVR for HTx are highlighted in Figure 1.

The lack of consensus regarding evaluation and management of elevated PVR in children with heart failure before HTx results in broad practice heterogeneity.[2] This scientific statement aims to review the available data on hemodynamics, pathophysiology, and management of PH secondary to left heart disease in children before and after HTx, identify knowledge gaps, and highlight areas for future research to identify and standardize best practices for optimal patient outcomes. Management of patients with single ventricle physiology is beyond the scope of this scientific statement and will not be discussed.

CLASSIFICATION AND PATHOBIOLOGY OF PH IN PEDIATRIC LEFT HEART DISEASE

Hemodynamic Definitions of PH

In 2018, the World Symposium on Pulmonary Hypertension (WSPH) issued a revision of the definition of PH from a mean pulmonary artery (PA) pressure (mPAP) ≥25 mm Hg to >20 mm Hg.[3] This was incorporated into the pediatric PH recommendations published by the WSPH in 2018[4] and the European Pediatric Pulmonary Vascular Disease Network,[5] although it is unclear whether a mild mPAP elevation of 21 to 24 mm Hg is clinically relevant in children and adolescents. Pulmonary arterial hypertension is classified as WSPH group 1 PH: a form of precapillary PH that is characterized by high mPAP with elevated PVR and normal PA wedge pressure (PAWP). In PH due to left heart disease (WSPH group 2), the major driver is systolic or diastolic dysfunction of the left ventricle, leading to LA hypertension and pulmonary venous congestion or hypertension, with elevated mPAP and PAWP (postcapillary PH). Congenital left-sided obstructive lesions, such as mitral or aortic valve stenosis, can also cause LA pressure elevation and postcapillary PH. Patients with postcapillary PH can develop elevated PVR, resulting in combined pre- and postcapillary PH with features of WSPH groups 1 and 2 (Table 1).

Classification of PH Due to Left Heart Disease

The broad diagnoses contributing to PH in left heart disease in children are presented in Figure 2, and include abnormalities anatomically located between the pulmonary capillaries and the thoracic descending aorta. Left heart failure can be further divided by LV ejection

Circulation: Heart Failure

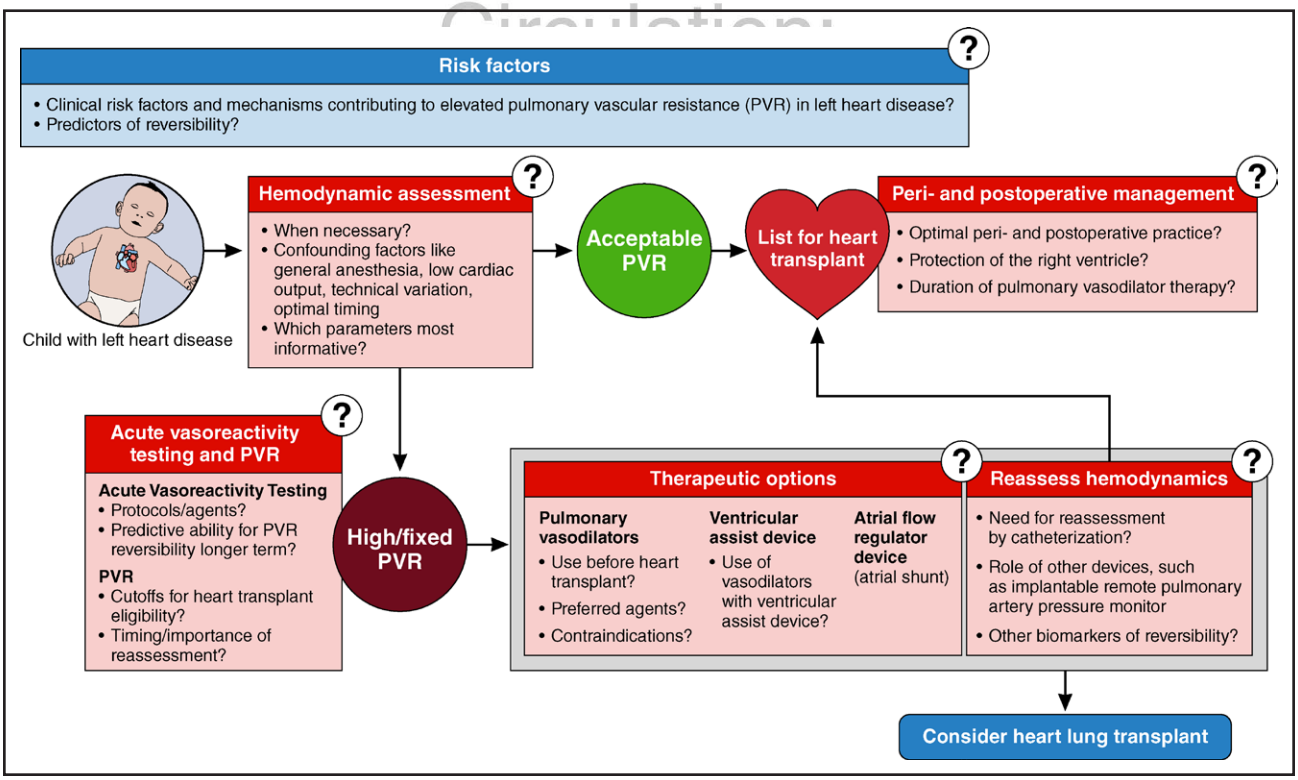

Figure 1. Clinical questions and management dilemmas in evaluation and treatment of children with left heart disease and elevated pulmonary vascular resistance.
Many questions remain regarding the approach to the pediatric patient with left heart disease and elevated pulmonary vascular resistance, including clinical risk factors, hemodynamic assessment by cardiac catheterization with acute vasoreactivity testing, and approach to medical management and transplant eligibility. The question marks highlight areas of uncertainty and practice heterogeneity that would benefit from further study.

Downloaded from http://ahajournals.org by on December 10, 2024

Table 1. Hemodynamic Definitions of Pulmonary Hypertension

Definitions*†	Invasive measures*†	WSPH group
Pulmonary hypertension (PH)*†	mPAP >20 mm Hg	1–5
Precapillary PH*† or pulmonary arterial hypertension	mPAP >20 mm Hg PAWP ≤15 mm Hg PVRi ≥3 WU m² (adults: PVR >2 WU‡)	1, 3, 4, and 5
Isolated postcapillary PH*†	mPAP >20 mm Hg PAWP >15 mm Hg PVRi <3 WU m² (adults: PVR <2 WU‡) dTPG <7 mm Hg (optional)	2 and 5
Combined post- and precapillary PH	mPAP >20 mm Hg PAWP >15 mm Hg PVRi ≥3 WU m² (adults: PVR >2 WU‡) dTPG ≥7 mm Hg (optional)	2 and 5

Hemodynamic definitions according to the 2018 World Symposium on Pulmonary Hypertension (WSPH)[3] and the 2022 European Society of Cardiology/European Respiratory Society guidelines on pulmonary hypertension (PH) in adults.[17] dTPG indicates diastolic transpulmonary pressure gradient; PAWP, pulmonary artery wedge pressure; and PVRi, pulmonary vascular resistance indexed for body surface area.

*The definitions of the PH subtypes apply only when cardiac index is either normal or decreased, and not in hyperdynamic states with substantially increased cardiac index (eg, high-dose prostacyclin analogue infusion, sepsis).

†The definition of PH has changed to a lower mean pulmonary arterial pressure (mPAP) cutoff value (mPAP >20 mm Hg) and now also includes the pulmonary vascular resistance cutoff value of 3 WU (adults) and 3 WU·m² (children) to distinguish precapillary from isolated postcapillary PH.

‡European Society of Cardiology/European Respiratory Society guidelines only.

Adapted with permission from Simonneau et al[3] and Humbert et al.[17] © Copyright 2023 European Respiratory Society.

Circulation. Heart Failure

fraction status (ie, heart failure with preserved ejection fraction versus heart failure with reduced ejection fraction [HFrEF]). According to the 2018 WSPH classification,[3] PH due to left heart disease (WSPH group 2 PH) includes the following subgroups:

2.1: PH due to heart failure with preserved ejection fraction
2.2: PH due to HFrEF
2.3: Valvular heart disease
2.4: Congenital/acquired cardiovascular conditions leading to postcapillary PH

Children can develop PH secondary to LV myocardial dysfunction or failure (systolic, diastolic, or both) or because of underlying congenital or acquired heart diseases with preserved or reduced LV ejection fraction.[6] In children, heart failure with preserved ejection fraction is most commonly associated with congenital hypoplasia of left-sided structures (such as the Shone complex, hypoplastic left heart variants, or restrictive cardiomyopathies) or congenital left inflow/outflow obstructive lesions (such as mitral stenosis, cor triatriatum, or chronic mitral regurgitation).[7] Rheumatic heart disease affecting the mitral valve is a common acquired cause of WSPH group 2 PH in low- to middle-income countries, but it is less common in developed nations.[8] Pulmonary vein stenosis is an important cause of WSPH group 2 PH, but it is not discussed in this article, because patients with pulmonary vein stenosis are not typically considered for isolated HTx. Congenital or acquired LV outflow obstructions, such as aortic stenosis or coarctation of the aorta, are more likely to present with HFrEF in children. Other causes of HFrEF include dilated and hypertrophic cardiomyopathies, which can be congenital/inherited or acquired.[7,9] In addition, patients with complex congenital heart disease (WSPH group 5.4 PH), such as Shone complex with shunts, can develop combined pre- and postcapillary PH of varying severity because of the variability in underlying hemodynamics and repair strategies.[3,4]

Pathobiology of PH in Left Heart Disease

Chronic pulmonary venous congestion and resulting PH can lead to constriction and remodeling of the pulmonary vasculature, resulting in elevated PVR (Figure 2). Precapillary vasoconstriction may be a protective reflex to prevent pulmonary edema when PA pressure is elevated because of congestion, at least in the early phases of disease.[10] The timing and precise mechanisms underlying PA remodeling remain unclear but likely include increased wall stress and myogenic contraction leading to smooth muscle cell proliferation, as well as genetic and metabolic factors.[11,12] This remodeling is characterized histologically by medial thickening of PAs and, less frequently, intimal fibrosis.[13] In children with pulmonary venous hypertension because of congenital mitral stenosis, extensive medial hypertrophy of the PAs has been reported,[14] with the medial thickness correlating with degree of PH.[15] Despite the severity of vascular remodeling in mitral stenosis, the PA pressure typically normalizes after surgical intervention, suggesting reversibility of vascular changes.[14,16] Given the high risk associated with lung biopsy in children with heart failure and PH, less invasive diagnostic tests are needed to characterize vascular remodeling before HTx and assess reversibility, such as serum biomarkers or advanced imaging modalities.

Epidemiology of PH in Pediatric Left Heart Disease

According to the 2022 European Society of Cardiology/European Respiratory Society guidelines, PH due to left heart disease represents the most prevalent form of PH in adults, accounting for 65% to 80% of cases.[17] However, epidemiologic and outcome data on PH due to left heart disease in children are sparse, because this population is rarely included in pediatric PH registries. A recent registry of children with acute decompensated heart failure admitted to cardiac intensive care units identified PH in 6% of hospital encounters, which was more common in patients with congenital heart disease than those without.[18] Differences in pathogenesis, age, severity, duration,

Downloaded from http://ahajournals.org by on December 10, 2024

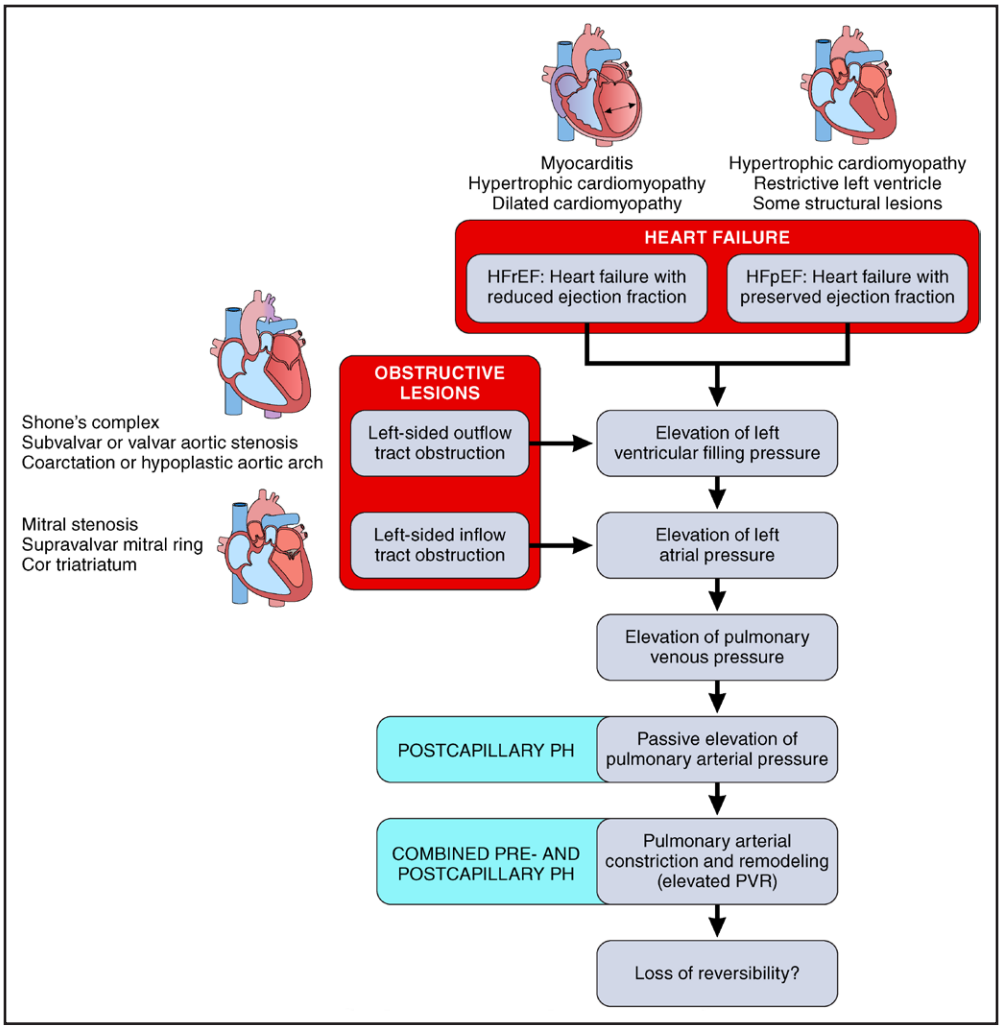

Figure 2. Mechanisms of pulmonary hypertension due to left heart disease.
Pathogeneses underlying left-sided heart disease in children and adolescents include both congenital and acquired structural anomalies of the left outflow and inflow tracts as well as primary causes of systolic and diastolic heart failure with both preserved and reduced ejection fraction. Elevation of pulmonary venous pressure is a common converging point for all pathogeneses, which is typically preceded by elevation of left atrial pressure. Elevations of pulmonary venous pressure are propagated onto the arterial side through alveolar capillaries, causing postcapillary pulmonary hypertension (PH). In the setting of chronic postcapillary PH, precapillary pulmonary vasoconstriction and arterial remodeling can give way to elevated pulmonary vascular resistance (PVR), causing combined pre- and postcapillary PH. Factors contributing to reversibility of PVR remain unclear.

and management of heart disease all likely affect the degree of severity and potential for reversibility of combined pre- and postcapillary PH in children.

HEMODYNAMIC CONSIDERATIONS FOR HTx

Cardiac Catheterization

Whereas cardiac catheterization is not recommended for routine surveillance in children before HTx, it is recommended in the setting of concern for PH.[19] Practice variation exists regarding cardiac catheterization for hemodynamic assessment before HTx because of lack of data to support recommendations but may be undertaken, at least in part, to differentiate between isolated postcapillary or combined pre- and postcapillary PH (Table 1), by PVR and other measures. The PVR is calculated as the mean transpulmonary pressure gradient divided by pulmonary blood flow. In children, PVR is indexed for body surface area (PVRi), and reported in indexed Wood units (iWU; mm Hg·L·min·m^2, WU·m^2). Despite potential usefulness, there may be limitations to pre-HTx invasive hemodynamic assessment in children, in terms of approach, calculations, and procedural risk, including the following: (1) accurate measurement of cardiac output may be challenging in the setting of severely reduced ventricular function or confounded by presence of a VAD; (2) there is no consensus regarding use of calculated Fick (usually with assumed oxygen consumption) versus measured thermodilution methods for determination of cardiac output[2]; (3) sedation or anesthesia for the

Downloaded from http://ahajournals.org by on December 10, 2024

procedure affects both pulmonary and systemic vascular resistance and does not reflect baseline conditions; (4) there is a lack of standardization of protocols for monitoring and pressure measurements; and (5) the procedure carries risk, especially in critically ill children.

The diastolic transpulmonary pressure gradient (dTPG), also called diastolic pressure gradient, is calculated by subtracting the PAWP from the diastolic PA pressure. Because dTPG is a directly measured indicator of precapillary pulmonary vascular disease, it is less sensitive to flow metrics (confounders) and largely independent of RV stroke volume. Studies in adults suggest dTPG is preferable for the assessment of the precapillary component in WSPH group 2 PH.[20,21] One pediatric study found high pre-HTx diastolic pressure indices (diastolic PA pressure and dTPG) were associated with higher risk of early graft loss after HTx, whereas PVRi was not.[22]

Acute Vasoreactivity Testing

Acute vasoreactivity testing (AVT) can be performed during cardiac catheterization to assess response of the pulmonary vascular bed to vasodilators and assess PH reversibility. The 2016 International Society for Heart Lung Transplantation guidelines recommend performing AVT if PA systolic pressure is ≥50 mm Hg and either transpulmonary pressure gradient is ≥15 mm Hg or PVR is >3 WU while maintaining systolic blood pressure >85 mm Hg.[19] There is no standardized approach to AVT in children before HTx. Most centers use inhaled nitric oxide (iNO) either alone or in combination with 100% oxygen, if they assess acute vasoreactivity in patients with elevated PVRi at baseline.[2] However, there is a paucity of data on the optimal approach. Patients with combined pre- and postcapillary PH may require a reduction in LV afterload to achieve optimization of PVRi, so some centers use nitroprusside or milrinone, either alone or in combination with iNO, to assess changes in PVRi.[23,24] The potential risk of AVT is acute pulmonary edema from worsening LA and pulmonary venous hypertension, although 1 study demonstrated that iNO decreased PA pressure and PVR in children with baseline LA pressure >15 mm Hg without a substantial increase in LA pressure.[25] Because there are no studies to guide absolute contraindications for AVT, clinicians should carefully weigh risks and benefits of testing patients with severe LA hypertension, especially in the setting of hemodynamic instability or preexisting pulmonary edema, and exercise caution if the PAWP is greatly elevated.

Unlike for WSPH group 1 PH (pulmonary arterial hypertension), there are no accepted definitions of positive AVT for WSPH group 2 PH. The 24th Bethesda conference stated that a PVR >6 WU that "decreases by 50% with hemodynamic maneuvers" was acceptable for orthotopic transplant, based on limited adult data at the time.[26] A recent practice survey of pediatric physicians revealed that half of responding centers consider a PVRi cutoff <6 iWU after AVT as acceptable to proceed with HTx.[2] However, PVRi alone may be insufficient to interpret hemodynamic response to AVT. For example, AVT usually increases pulmonary blood flow (denominator) but may also lead to a disproportionate rise in LA pressure (and PAWP) if there is unmasked LV diastolic dysfunction. This causes a decrease in mean transpulmonary pressure gradient (numerator), and, as such, the PVRi. The drop in the calculated PVRi may then be more reflective of restrictive LV physiology than vasoreactivity and would indicate a contraindication to pulmonary vasodilator use. For this reason, PVRi must be considered in context of complete hemodynamic data. Some centers include both transpulmonary pressure gradient (mean, diastolic, or both) and PVRi[27–30] as criteria in HTx evaluation. Clinical experience suggests lack of response to AVT may not preclude response to longer-term pulmonary vasodilator therapy, and, conversely, a reactive vascular bed may become unresponsive over time. Considerations affecting response to longer-term pulmonary vasodilator therapy may include AVT response, but also other factors, such as the patient's age (eg, <1 year is more reversible[30]), underlying diagnosis, duration of left heart disease, and other comorbidities, including lung disease, previous post-tricuspid shunt, or genetic conditions.

Circulation: Heart Failure

PVR AND HTx OUTCOMES

Since the 24th Bethesda conference in 1993 recommended fixed PVR >6 WU as an exclusion criterion for HTx, a number of pediatric studies have evaluated the effect of elevated PVRi on post-HTx outcomes, primarily retrospective cohort studies of patients from the mid-1980s to early 2000s. Some reported a strong statistical association between elevated pretransplant PVRi and mortality risk,[27–29,31,32] whereas others found no effect of PVRi on outcomes[32–36] (Table 2).

Reasons for the striking discrepancies remain unclear, but likely reflect heterogeneity of patient populations, analysis methods, PVRi cutoffs used, inclusion of AVT, post-HTx management, outcomes evaluated, and time period. There is no clear era effect of elevated PVRi affecting outcomes more greatly before widespread availability of VADs and pulmonary vasodilator therapies.

Few studies have examined whether post-HTx death resulted from right heart failure or PH and lack consensus regarding whether elevated pre-HTx PVRi corresponded to post-HTx RV failure.[29,31] One recent study found no association between elevated PVRi and graft failure, instead finding the presence of multiple high-risk clinical criteria to be predictive.[34] Another study correlated increasing number of high-risk clinical factors with cumulative mortality risk.[33] In addition to PVRi, contributors may include primary cardiac diagnosis, mechanical circulatory support, end organ dysfunction, comorbidities,

Downloaded from http://ahajournals.org by on December 10, 2024

Table 2. Studies Reporting Outcomes of Pediatric Patients With Elevated Pulmonary Vascular Resistance Before Heart Transplant

Study	Years	N	Age range	PVRi cutoff (WU·m²)	AVT included	Conclusions
Addonizio et al[36] (1989)	1984–1988	30	5 d–18 y	6	No	No difference in mortality rates in patients with elevated PVR unless high PVR was combined with inotrope dependence (1-y survival 30% vs 84% in those without either risk factor)
Bando et al[27] (1993)	1982–1992	67	1 d–18 y	4 and TPG >15 mm Hg	No	Elevated TPG was a risk factor for early (30-d) death
Huang et al[28] (2004)	1986–2001	165	0–22 y	6 and TPG <15 mm Hg	Yes	Risk of isolated RV graft failure increased by 1.2-fold for every 1 iWU in maximal PVR
Davies et al[33] (2008)	1995–2005	3502	0–21 y	6	No	PVRi >6 alone was not associated with early (<30 d) or late (1 y) death
Hoskote et al[29] (2010)	2000–2006	129	0–18 y	6 and TPG <15 mm Hg	Yes	PVRi >6 (despite reactivity) and RCM diagnosis predicted postoperative RV failure; PVRi (but not RV failure) independently predicted long-term survival
Ofori-Amanfo et al[31] (2011)	1984–2005	263	0.1–25.4 y	6	Yes	Elevated PVR was associated with worse 3-mo, 1-y, and overall survival; AVT nonresponders had increased risk of right heart failure after HTx
Auerbach et al[34] (2012)	1993–2006	189	0–23.6 y	6	Yes	PVRi >6 (reactive or not) was not a significant risk factor for graft loss
Buddhe et al[30] (2012)	1994–2010	1322	0–18 y	TPG >12	No	Increased mortality rate at 1 and 3 mo in recipients with PH >1 y of age; no effect on mortality rate in children <1 y of age; no improvement with recent availability of pulmonary vasodilator therapy
Chiu et al[37] (2012)	1984–2010	158	0.3–17.8 y	6	Yes	ROC analysis identified PVRi 929 iWU and AUC 0.863 as optimal cutoff for risk of increased 30-d mortality (AUC 0863); no clear effect of vasoreactivity
Chiu et al[35] (2015)	1987–2011	1943	0–18 y	6, 9	No	PVRi was not a significant predictor of outcomes; no survival difference with propensity-matched HTx recipients
Maxwell et al[32] (2015)	2002–2012	3523	0–18 y	3.37	No	ROC analysis identified PVRi 337 iWU (AUC 0.69) as dichotomized variable predicting early (30-d) death, but not as continuous variable
Richmond et al[38] (2015)	1993–2011	1909	0.1–18 y	NA	No	In pediatric HTx recipients without congenital heart disease, elevated PVRi did not affect survival after HTx; pre-HTx PVRi >5 iWU in 24% of cohort
Balakrishnan et al[39] (2021)	2014–2019	97	1–18 y	4	No	PVR had no effect on early or late survival in single-center cohort

AUC indicates area under the curve; AVT, acute vasoreactivity testing; HTx, heart transplantation; iWU, indexed Wood units; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance indexed for body surface area; RCM, restrictive cardiomyopathy; ROC, receiver operating characteristic; RV, right ventricle; and TPG, transpulmonary gradient.

Circulation: Heart Failure
American Heart Association.

Downloaded from http://ahajournals.org by on December 10, 2024

donor matching considerations, and immunosuppression modalities. This begs the question as to whether the earlier outcomes studied resulted directly from elevated PVRi or if PVRi may, in part, have served as a surrogate for duration or severity of heart failure. Another recent study found no effect of PVRi on post-HTx outcomes, but included only a few patients with PVRi >6 iWU.[39] However, if centers apply empiric PVRi cutoffs, the usefulness of retrospective studies may be limited. Patients with elevated PVRi are often managed differently than patients with low PVRi, with intensive pulmonary vasodilator therapy and mechanical support, the details of which are not always reported in database or registry-based studies. Therefore, the lack of association between PVRi and post-HTx mortality risk in a large, multicenter pediatric cohort of >1900 children that included 24% with PVRi >5 iWU primarily suggests that current management strategies can be successful to overcome elevated PVRi to facilitate HTx.[38]

There remains a lack of consensus regarding whether, or to what degree, PVR elevation should be considered relevant for HTx with respect to post-HTx mortality risk.[35] Because the therapeutic landscape has changed considerably since the 1980s with the use of VADs, additional medical therapies for heart failure, and widespread use of pulmonary vasodilators, studies are needed in the current era to guide interpretation and management of elevated PVRi in children before HTx and promote a more nuanced approach that accounts for multiple risk factors.

THERAPIES TO TREAT PH: MEDICATIONS, DEVICES, AND MECHANICAL SUPPORT

Pretransplant Management of Elevated PVR

In the pediatric HTx candidate with elevated PVR, goals of therapy often focus on establishing or improving transplant candidacy by lowering PVR and improving heart failure symptoms, although there is no consensus regarding approach to the use of combined heart failure therapies and pulmonary vasodilators. Initial strategies focus on optimization of hemodynamics to reduce LA

pressure and mPAP. Chronic inotropic therapy, such as with intravenous milrinone, has been shown to improve cardiac index, PAWP, and PVR in adults with heart failure.[40] Many transplant centers use LV assist devices (LVADs) for advanced heart failure support. In adult studies, LVAD use reduces PH acutely, and may lower even a fixed PVR over time (ie, precapillary) by allowing the pulmonary vascular bed to remodel under more favorable hemodynamic conditions.[41,42] One recent pediatric study showed improved waitlist outcomes for children receiving mechanical support before HTx regardless of PVR.[43] Whether LVAD implantation alone may be sufficient for lowering PVR in children remains unclear.

Guidelines do not recommend routine use of pulmonary vasodilators in WSPH group 2 because of lack of evidence and risk of clinical worsening,[5,17,44] but real-world clinical practice is heterogenous, and PH medications are used by some centers to reduce PVR before HTx.[2,45] Pulmonary vasodilators target 3 main pathways: NO (phosphodiesterase type 5 inhibitors or soluble guanylate cyclase stimulators), endothelin (endothelin receptor antagonists), and prostaglandin I_2 (prostanoids).[5] Studies of pulmonary vasodilators in children before HTx are limited to retrospective case series, but may suggest benefit for lowering PVRi without clinically relevant worsening.[45] In a recent pediatric cohort of 22 children with WSPH group 2 PH, the phosphodiesterase type 5 inhibitor sildenafil was associated with improved RV metrics, albeit with 2 discontinuations for pulmonary edema.[46] Although the goal is often to lower PVR, a recent study showed that the parenteral prostanoid treprostinil also improved heart failure symptoms without increases in LA pressure in a single-center pediatric cohort.[47] Soluble guanylate cyclase stimulators may affect both PVR and heart failure: riociguat is used as a therapy for pulmonary arterial hypertension,[48] and vericiguat was recently shown to improve cardiovascular hospitalization and mortality rates in adults with HFrEF (PH was not evaluated in this study).[49] A clinical trial of vericiguat in pediatric patients with heart failure is underway (Efficacy, Safety, and Pharmacokinetics of Vericiguat in Pediatric Participants With Heart Failure Due to Left Ventricular Systolic Dysfunction [MK-1242-036].[50]

Despite some reports of benefit, pulmonary vasodilators carry the risk of worsening LA hypertension because of increased transpulmonary blood flow, which can lead to pulmonary edema, systemic arterial hypotension, and potentially reduced coronary perfusion. Endothelin receptor antagonists bosentan and macitentan worsened fluid retention in adults with HFrEF.[51,52] Dedicated studies of pulmonary vasodilator use in pediatric WSPH group 2 PH are needed to determine safety and efficacy of these agents in children and guide clinical practice.

In some cases, LVAD placement is combined with pulmonary vasodilators to optimize PVR and minimize RV afterload, with the goal of avoiding the need for right-sided VAD. It may be difficult to predict preoperatively whether right VAD will be needed (in addition to LVAD). Although attempts have been made to validate adult criteria for biventricular VADs in pediatrics, no specific predictor for RV failure has yet been identified.[53] Many pediatric centers begin with LVAD combined with pulmonary vasodilator therapy in the operating room (often oxygen and iNO) while evaluating right ventricular performance by echocardiogram in real time.[54]

After LVAD, some centers change or add pulmonary vasodilators for longer-term use. Recent survey data suggest clinicians are more inclined to use PH medications when an LVAD is in place.[2] In a cohort of 17 pediatric patients with a VAD receiving prostacyclins, and some also receiving phosphodiesterase type 5 inhibitors, there was a significant reduction in inotrope need within the first 24 postoperative hours with minimal adverse effects.[55] Clinical experience suggests that with therapy (LVAD, vasodilators, or both), PVR can improve over weeks to months while awaiting HTx, but further study is needed to determine optimal practice regarding clinical indications for therapies and which specific therapies are most beneficial.

Some patients are not suitable candidates for VADs, such as those with small ventricular cavities because of restrictive cardiomyopathy or congenital heart malformations not amenable to cannula placement.[56] Recent clinical trials of transcatheter implantable atrial flow regulators for heart failure with preserved ejection fraction and HFrEF in adults have indicated improved survival.[57,58] Use of atrial flow regulators to create a restrictive left-to-right atrial shunt in children with restrictive cardiomyopathy, LA hypertension, and PH has recently been reported in a limited number of cases, with promising effects on symptoms and hemodynamics.[59] However, the long-term effect of a restrictive left-to-right atrial shunt is unknown, and these devices are not widely available for use in the United States. In some centers, atrial flow regulator device implantation may be considered as a bridge to HTx in young patients with restrictive cardiomyopathy or as destination therapy in those who are not HTx candidates. Potts shunt (pulmonary to systemic arterial connection) with atrial septostomy has also been proposed as a potential therapy for PH in left heart disease.[60]

Regardless of therapy, PH can be dynamic in left heart disease, and repeat cardiac catheterization may be necessary after initiation of medical or LVAD therapy. Whereas pediatric data are limited, 3 to 6 months is the suggested timing for reevaluation of hemodynamics after LVAD placement with elevated PVR, although shorter timeframes may be appropriate, especially for patients with paracorporeal support devices.[19] The need for and appropriate frequency of hemodynamic reassessment by cardiac catheterization is unknown given the risks of the procedure and the lack of data

Downloaded from http://ahajournals.org by on December 10, 2024

Circulation: Heart Failure

to support the effect on outcomes. The usefulness of repeat AVT in patients already on pulmonary vasodilator therapy is unclear but could be considered to ascertain potential benefit of additional agents. For those with paracorporeal VADs, decreased right VAD emptying or poor LVAD filling may be indicators of increased PVR impeding blood transit through the pulmonary vascular bed with inadequate unloading of the LA. The recent development of an implantable remote PA pressure monitoring device, which has been used in patients as young as 9 years, has allowed for repeatable noninvasive pressure measurements at the bedside or in the outpatient setting.[61]

Nursing and Allied Health Professionals

Nurses and allied health professionals are part of a multidisciplinary team to optimize successful treatment of PH before HTx in both the inpatient and outpatient settings. For inpatients, bedside nurses are often the first to identify changes in patient status or VAD flows, and may be first on hand in case of emergency.[62] Rehabilitation both before and after transplant may include nutritional assessment and support, as well as physical, occupational, speech, and feeding therapies to improve quality of life.[63,64] Many patients and families experience difficulties in psychologic well-being and adjustment, especially regarding VAD therapy, and benefit from support from social workers, child life specialists, palliative care specialists, and psychologists. For home pulmonary vasodilator therapies, advanced practitioners and nurses can work with pharmacists to provide education on medication administration and complication identification, navigate insurance barriers to off-label use, and coordinate with outpatient specialty pharmacies to ensure no lapses in treatment.

Operative Considerations

There are important operative considerations when performing HTx in pediatric patients with elevated PVR. A short donor ischemic time is considered favorable. The historical practice of selecting hearts with higher donor-recipient weight ratios for recipients with elevated PVR has been challenged as studies showed no post-transplant survival benefit in patients with an oversized heart and no increased risk of death with an undersized organ.[65,66]

Mechanical circulatory support is used frequently as a bridge to HTx in children,[67] balancing risks of bleeding, thromboembolism, infection, human leukocyte antigen immunization, and longer operative time against potential benefits in growth, psychomotor development, end organ function, and hemodynamics. In a recent study, the presence of elevated PVR did not diminish the beneficial wait list outcomes for those patients bridged to HTx on mechanical support.[43]

Appropriate preoperative PH treatment does not guarantee a smooth postoperative course, so perioperative management strategies to lower pulmonary pressures and relieve stress on the sensitive donor RV are important. These may include oxygen, iNO, milrinone, diuresis, early extubation, and the avoidance of bleeding (with transfusion as needed) to protect the RV in the immediate postoperative period. Whereas early extubation may be desired to minimize the effects of positive pressure ventilation on RV preload and afterload, some patients with elevated PVR are at high risk for PH crisis and acute RV failure in the immediate postoperative period, such that empiric analgesia and sedation with mechanical ventilatory support may be necessary for a prolonged period after HTx.[37] In some cases, it may be prudent to leave the chest open or consider mechanical support in cases of refractory right heart failure. Creating an individualized postoperative management plan with vasodilator therapy is site-specific, with some variability.

Postoperative Management

In most cases, PVR drops quickly after HTx, often within weeks. The optimal duration of pulmonary vasodilator therapy after HTx remains poorly understood, but can be guided by hemodynamic assessments performed at the time of endomyocardial biopsy. If a remote PA pressure monitoring device was implanted before transplant, its continued use can also help guide duration and intensity of treatment.

Pulmonary vasodilators are often continued in patients receiving them preoperatively, but practice varies between centers.[2] Endothelin receptor antagonists pose specific risk for drug-drug interactions with immunosuppressive agents because of cytochrome P450 enzyme effects. Bosentan has the most drug interactions because of CYP3A4 inhibition, and its use is contraindicated with certain agents, including cyclosporine, or dose adjustments may be needed with other medications. Macitentan and ambrisentan have fewer known drug interactions but clinicians should be aware of potential effects of any of the endothelin receptor antagonists on concomitant therapies and monitor drug levels or adjust therapies accordingly.[68]

When concomitant reduction of systemic blood pressure is needed and graft LV systolic function is preserved, some centers use calcium channel blockers given the effect of calcium channel blockade on vasoreactive pulmonary arterial hypertension (WSPH group 1 PH).[4,5,69] However, the potential benefit is theoretical; no studies have described the effect of calcium channel blockers on PVR after HTx. Although there are no recommendations regarding duration of therapy, most patients discontinue PH treatment within a few months, and it is unusual to need to reinitiate therapy once discontinued.

Circulation: Heart Failure

Downloaded from http://ahajournals.org by on December 10, 2024

CONCLUSIONS

Children with left heart disease are at risk for developing PH with elevated PVR, but knowledge gaps exist regarding clinical and hemodynamic prognostic factors. The risk of elevated PVR for poor HTx outcome was recognized in the early days of pediatric HTx. However, most studies evaluating risk of preoperative elevated PVR were performed during a time when the therapeutic options were limited, and these studies lacked consensus regarding PVR cutoffs for HTx and importance of vasoreactivity. More recent studies fail to show a substantial risk of elevated PVRi on post-HTx outcomes, but are limited by their retrospective nature and heterogeneity of approach to pulmonary vasodilator use and HTx listing. Despite insufficient evidence in the current era, some pediatric centers still use a post-AVT PVRi of <6 iWU for HTx eligibility. Because of the many confounders in PVRi assessment in children with left heart disease, it is likely that a combination of hemodynamic and clinical variables for eligibility assessment would better predict risk. Practice regarding use of pulmonary vasodilators, with and without LVAD, remains heterogeneous without sufficient pediatric data to guide practice. Because a donor RV may be greatly sensitive to high afterload, close monitoring and aggressive treatment of elevated PVR is often required in the early postoperative period.

We highlight the following controversies and knowledge gaps in the care of children with elevated PVR before HTx:

- Prevalence of elevated PVR in pediatric left heart disease
- Clinical risk factors for developing elevated PVR and biomarkers of reversibility
- Importance and caveats of calculated PVRi in determining HTx eligibility and potential role for other surrogates, such as dTPG
- When cardiac catheterization is indicated or necessary and when procedural risk may outweigh benefit
- Standardization of protocols for hemodynamic assessment by cardiac catheterization, including criteria and methods for performing AVT
- Predictive value of AVT in determining response to longer-term vasodilator therapy
- Whether, and when, pulmonary vasodilator therapy is indicated, and considerations when LVAD is in place
- Which pulmonary vasodilators may be preferential for combined pre- and postcapillary PH in children
- Optimal perioperative management strategies regarding elevated PVR at time of HTx
- Duration of pulmonary vasodilator use after HTx

Prospective multicenter studies are needed to evaluate management strategies and produce consensus recommendations to guide practice, standardize care, and ensure equitable and optimal outcomes for children undergoing HTx.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on August 30, 2024, and the American Heart Association Executive Committee on September 23, 2024. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Hopper RK, Hansmann G, Hollander SA, Dipchand AI, van der Have O, Iler C, Herrington C, Rosenzweig EB, Alejos JC, Tran-Lundmark K; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative & Resuscitation; Council on Clinical Cardiology; and Council on Cardiovascular Stroke Nursing. Clinical management and transplant considerations in pediatric pulmonary hypertension due to left heart disease: a scientific statement from the American Heart Association. *Circ Heart Fail.* 2024;17:e•••–e•••. doi: 10.1161/HHF.0000000000000086

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at https://www.heart.org/permissions. A link to the "Copyright Permissions Request Form" appears in the second paragraph (https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form).

Acknowledgment

The authors thank information specialist Matthias Bank, Library & ICT, Faculty of Medicine, Lund University, Sweden, for assistance with the comprehensive literature search and article retrieval.

Downloaded from http://ahajournals.org by on December 10, 2024

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Rachel K. Hopper	Stanford University School of Medicine	None	None	None	None	None	None	None
Karin Tran-Lundmark	Lund University/Skane University Hospital (Sweden)	None	None	None	None	None	None	None
Juan C. Alejos	UCLA Mattel Children's Hospital	None	None	None	None	None	None	None
Anne I. Dipchand	University of Toronto/Hospital for Sick Children (Canada)	None	None	None	None	None	None	None
Georg Hansmann	University Hospital Erlangen (Germany)	None	None	None	None	None	None	None
Cynthia Herrington	Children's Hospital Los Angeles	None	None	None	None	None	None	None
Seth A. Hollander	Stanford University School of Medicine	None	None	Shanghai Pediatric Cardiology Summit*	None	None	None	None
Colleen Iler	Children's National Hospital	None	None	None	None	None	None	None
Erika B. Rosenzweig	Westchester Medical Center Network and New York Medical College	None	None	None	None	None	None	None
Oscar van der Have	Lund University/Skane University Hospital (Sweden)	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Scott R. Auerbach	University of Colorado School of Medicine, Children's Hospital Colorado Heart Institute	None	None	None	None	None	None	None
Jonathan M. Chen	Children's Hospital of Philadelphia	None	None	None	None	None	None	None
D. Dunbar Ivy	University of Colorado Health Sciences Center	NIH (Co-Investigator)*	Janssen* (The University of Colorado consults with Janssen for Dr Ivy to perform clinical research trials); Merck* (The University of Colorado contracts with Merck for Dr Ivy to perform clinical trials)	None	None	None	Janssen*; Merck*	None
David Ming-Shen Peng	University of Michigan	None	None	None	None	None	None	None
Joseph W. Rossano	Children's Hospital of Philadelphia/University of Pennsylvania	None	None	None	None	None	Merck*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

REFERENCES

1. Bhatia SJ, Kirshenbaum JM, Shemin RJ, Cohn LH, Collins JJ, Di Sesa VJ, Young PJ, Mudge GH Jr, Sutton MG. Time course of resolution of pulmonary hypertension and right ventricular remodeling after orthotopic cardiac transplantation. *Circulation*. 1987;76:819–826. doi: 10.1161/01.cir.76.4.819
2. Hopper RK, van der Have O, Hollander SA, Dipchand AI, Perez de Sa V, Feinstein JA, Tran-Lundmark K. International practice heterogeneity in pre-transplant management of pulmonary hypertension related to pediatric left heart disease. *Pediatr Transplant*. 2023;27:e14461. doi: 10.1111/petr.14461
3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated

Downloaded from http://ahajournals.org by on December 10, 2024

clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53:1801913. doi: 10.1183/13993003.01913-2018
4. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger RMF. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J.* 2019;53:1801916. doi: 10.1183/13993003.01916-2018
5. Hansmann G, Koestenberger M, Alastalo T-P, Apitz C, Austin ED, Bonnet D, Budts W, D'Alto M, Gatzoulis MA, Hasan BS, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN). *J Heart Lung Transplant.* 2019;38:879–901. doi: 10.1016/j.healun.2019.06.022
6. Jone PN, Ivy DD, Hauck A, Karamlou T, Truong U, Coleman RD, Sandoval JP, Del Cerro Marín MJ, Eghtesady P, Tillman K, et al. Pulmonary hypertension in congenital heart disease: a scientific statement from the American Heart Association. *Circ Heart Fail.* 2023;16:e00080. doi: 10.1161/HHF.0000000000000080
7. Amdani S, Conway J, George K, Martinez HR, Asante-Korang A, Goldberg CS, Davies RR, Miyamoto SD, Hsu DT; American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Surgery and Anesthesia; and Council on Cardiovascular and Stroke Nursing. Evaluation and management of chronic heart failure in children and adolescents with congenital heart disease: a scientific statement from the American Heart Association. *Circulation.* 2024;150:e33–e50. doi: 10.1161/CIR.0000000000001245
8. Hasan B, Hansmann G, Budts W, Heath A, Hoodbhoy Z, Jing Z-C, Koestenberger M, Meinel K, Mocumbi AO, Radchenko GD, et al; European Pediatric Pulmonary Vascular Disease Network (EPPVDN). Challenges and special aspects of pulmonary hypertension in middle- to low-income regions: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:2463–2477. doi: 10.1016/j.jacc.2020.03.047
9. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, Hsu DT, Lin KY, Price JF, Wilkinson JD, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. *Circulation.* 2019;140:e9–e68. doi: 10.1161/CIR.0000000000000682
10. Adatia I, Kulik T, Mullen M. Pulmonary venous hypertension or pulmonary hypertension due to left heart disease. *Prog Pediatr Cardiol.* 2009;27:35–42. doi: 10.1016/j.ppedcard.2009.09.006
11. Kulik TJ. Pulmonary hypertension caused by pulmonary venous hypertension. *Pulm Circ.* 2014;4:581–595. doi: 10.1086/678471
12. Brittain EL, Thenappan T, Huston JH, Agrawal V, Lai Y-C, Dixon D, Ryan JJ, Lewis EF, Redfield MM, Shah SJ, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; and Stroke Council. Elucidating the clinical implications and pathophysiology of pulmonary hypertension in heart failure with preserved ejection fraction: a call to action. *Circulation.* 2022;146:e73–e88. doi: 10.1161/CIR.0000000000001079
13. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension guidelines from the American Heart Association and American Thoracic Society. *Circulation.* 2015;132:2037–2099. doi: 10.1161/CIR.0000000000000329
14. Haworth SG. Pulmonary vascular disease in different types of congenital heart disease: implications for interpretation of lung biopsy findings in early childhood. *Br Heart J.* 1984;52:557–571. doi: 10.1136/hrt.52.5.557
15. Endo M, Yamaki S, Ohmi M, Tabayashi K. Pulmonary vascular changes induced by congenital obstruction of pulmonary venous return. *Ann Thorac Surg.* 2000;69:193–197. doi: 10.1016/s0003-4975(99)01079-6
16. Kulik TJ, Harris JE, McElhinney DB. The impact of pulmonary venous hypertension on the pulmonary circulation in the young. *Congenit Heart Dis.* 2011;6:603–607. doi: 10.1111/j.1747-0803.2011.00580.x
17. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J.* 2023;61:2200879. doi: 10.1183/13993003.00879-2022
18. Lasa JJ, Gaies M, Bush L, Zhang W, Banerjee M, Alten JA, Butts RJ, Cabrera AG, Checchia PA, Elhoff J, et al. Epidemiology and outcomes of acute decompensated heart failure in children. *Circ Heart Fail.* 2020;13:e006101. doi: 10.1161/CIRCHEARTFAILURE.119.006101
19. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, et al; International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;35:1–23. doi: 10.1016/j.healun.2015.10.023
20. Naeije R, Vachiery J-L, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J.* 2013;41:217–223. doi: 10.1183/09031936.00074312
21. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest.* 2013;143:758–766. doi: 10.1378/chest.12-1653
22. Albers EL, Bradford MC, Friedland-Little JM, Hong BJ, Kemna MS, Chen JM, Law YM. Diastolic pressure indices offer a novel approach to predicting risk of graft loss after pediatric heart transplant. *Pediatr Transplant.* 2018;22:e13126. doi: 10.1111/petr.13126
23. Pasero D, Rana NK, Bonato R, Ribezzo M, Ivaldi F, Ricci D, Grosso Marra W, Checco L, Lupo M, Boffini M, et al. Inhaled nitric oxide versus sodium nitroprusside for preoperative evaluation of pulmonary hypertension in heart transplant candidates. *Transplant Proc.* 2013;45:2746–2749. doi: 10.1016/j.transproceed.2013.07.044
24. Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol.* 1996;28:1775–1780. doi: 10.1016/S0735-1097(96)00399-3
25. Adatia I, Perry S, Landzberg M, Moore P, Thompson JE, Wessel DL. Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. *J Am Coll Cardiol.* 1995;25:1656–1664. doi: 10.1016/0735-1097(95)00048-9
26. Mudge GH, Goldstein S, Addonizio LJ, Caplan A, Mancini D, Levine TB, Ritsch ME, Stevenson LW. 24th Bethesda conference: cardiac transplantation: task force 3: recipient guidelines/prioritization. *J Am Coll Cardiol.* 1993;22:21–31. doi: 10.1016/0735-1097(93)90812-f
27. Bando K, Konishi H, Komatsu K, Fricker FJ, del Nido PJ, Francalancia NA, Hardesty RL, Griffith BP, Armitage JM. Improved survival following pediatric cardiac transplantation in high-risk patients. *Circulation.* 1993;88:II218–II223.
28. Huang J, Trinkaus K, Huddleston CB, Mendeloff EN, Spray TL, Canter CE. Risk factors for primary graft failure after pediatric cardiac transplantation: importance of recipient and donor characteristics. *J Heart Lung Transplant.* 2004;23:716–722. doi: 10.1016/j.healun.2003.08.001
29. Hoskote A, Carter C, Rees P, Elliott M, Burch M, Brown K. Acute right ventricular failure after pediatric cardiac transplant: predictors and long-term outcome in current era of transplantation medicine. *J Thorac Cardiovasc Surg.* 2010;139:146–153. doi: 10.1016/j.jtcvs.2009.08.020
30. Buddhe S, Du W, L'Ecuyer T. Impact of pulmonary hypertension on transplant outcomes in pediatric cardiomyopathy patients. *Pediatr Transplant.* 2012;16:367–372. doi: 10.1111/j.1399-3046.2012.01678.x
31. Ofori-Amanfo G, Hsu D, Lamour JM, Mital S, O'Byrne ML, Smerling AJ, Chen JM, Mosca R, Addonizio LJ. Heart transplantation in children with markedly elevated pulmonary vascular resistance: impact of right ventricular failure on outcome. *J Heart Lung Transplant.* 2011;30:659–666. doi: 10.1016/j.healun.2010.12.007
32. Maxwell BG, Sheikh AY, Ajuba-Iwuji CC, Heitmiller ES, Vricella LA. Pulmonary vascular resistance index and mortality after paediatric heart transplant. *Cardiol Young.* 2015;25:1141–1147. doi: 10.1017/S1047951114001796
33. Davies RR, Russo MJ, Mital S, Martens TM, Sorabella RS, Hong KN, Gelijns AC, Moskowitz AJ, Quaegebeur JM, Mosca RS, et al. Predicting survival among high-risk pediatric cardiac transplant recipients: an analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg.* 2008;135:147–155, 155.e1. doi: 10.1016/j.jtcvs.2007.09.019
34. Auerbach SR, Richmond ME, Chen JM, Mosca RS, Quaegebeur JM, Addonizio LJ, Hsu DT, Lamour JM. Multiple risk factors before pediatric cardiac transplantation are associated with increased graft loss. *Pediatr Cardiol.* 2012;33:49–54. doi: 10.1007/s00246-011-0077-7
35. Chiu P, Schaffer JM, Sheikh AY, Ha R, Reinhartz O, Mainwaring R, Reitz BA. Elevated pretransplant pulmonary vascular resistance index does not predict mortality after isolated orthotopic heart transplantation in children: a retrospective analysis of the UNOS database. *Pediatr Transplant.* 2015;19:623–633. doi: 10.1111/petr.12550

Downloaded from http://ahajournals.org by on December 10, 2024

Circulation: Heart Failure

36. Addonizio LJ, Hsu DT, Fuzesi L, Smith CR, Rose EA. Optimal timing of pediatric heart transplantation. *Circulation*. 1989;80:III84–III89.
37. Chiu P, Russo MJ, Davies RR, Addonizio LJ, Richmond ME, Chen JM. What is high risk? Redefining elevated pulmonary vascular resistance index in pediatric heart transplantation. *J Heart Lung Transplant*. 2012;31:61–66. doi: 10.1016/j.healun.2011.08.021
38. Richmond ME, Law YM, Das BB, Everitt MD, Kukreja M, Naftel DC, Kemna MS, Henderson HT, Beddows K, Fricker FJ, et al; Pediatric Heart Transplant Study Investigators. Elevated pre-transplant pulmonary vascular resistance is not associated with mortality in children without congenital heart disease: a multicenter study. *J Heart Lung Transplant*. 2015;34:448–456. doi: 10.1016/j.healun.2014.04.021
39. Balakrishnan KR, Rao KGS, Subramaniam GK, Tanguturu MK, Arvind A, Ramanan V, Dhushyanthan J, Ramasubramanian K, Kumaran KS, Sellamuthu G, et al. Clinical profiles and risk factors for early and medium-term mortality following heart transplantation in a pediatric population: a single-center experience. *Ann Pediatr Cardiol*. 2021;14:42–52. doi: 10.4103/apc.APC_129_20
40. Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, Loyaga-Rendon RY, George JF, Acharya D. Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. *Circ Heart Fail*. 2015;8:880–886. doi: 10.1161/CIRCHEARTFAILURE.114.001778
41. Zimpfer D, Zrunek P, Roethy W, Czerny M, Schima H, Huber L, Grimm M, Rajek A, Wolner E, Wieselthaler G. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. *J Thorac Cardiovasc Surg*. 2007;133:689–695. doi: 10.1016/j.jtcvs.2006.08.104
42. Ozturk P, Engin AY, Nalbantgil S, Oguz E, Ayik F, Engin C, Yagdi T, Erkul S, Balcioglu O, Ozbaran M. Comparison of continuous-flow and pulsatile-flow blood pumps on reducing pulmonary artery pressure in patients with fixed pulmonary hypertension. *Artif Organs*. 2013;37:763–767. doi: 10.1111/aor.12164
43. Thangappan K, Morales DLS, Vu Q, Lehenbauer D, Villa C, Wittekind S, Hirsch R, Lorts A, Zafar F. Impact of mechanical circulatory support on pediatric heart transplant candidates with elevated pulmonary vascular resistance. *Artif Organs*. 2021;45:29–37. doi: 10.1111/aor.13747
44. Vachiéry J-L, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, Marco TD. Pulmonary hypertension due to left heart disease. *Eur Respir J*. 2019;53:1801897. doi: 10.1183/13993003.01897-2018
45. Daftari B, Alejos JC, Perens G. Initial experience with sildenafil, bosentan, and nitric oxide for pediatric cardiomyopathy patients with elevated pulmonary vascular resistance before and after orthotopic heart transplantation. *J Transplant*. 2010;2010:656984. doi: 10.1155/2010/656984
46. Desai K, Di Lorenzo M, Zuckerman WA, Emeruwa E, Krishnan US. Safety and efficacy of sildenafil for group 2 pulmonary hypertension in left heart failure. *Children (Basel)*. 2023;10:270. doi: 10.3390/children10020270
47. Hollander SA, Ogawa MT, Hopper RK, Liu E, Chen S, Rosenthal DN, Feinstein JA. Treprostinil improves hemodynamics and symptoms in children with mild pulmonary hypertension awaiting heart transplantation. *Pediatr Transplant*. 2020;24:e13742. doi: 10.1111/petr.13742
48. García Aguilar H, Gorenflo M, Ivy DD, Moledina S, Castaldi B, Ishida H, Cześniewicz P, Kusa J, Miera O, Pattathu J, et al. Riociguat in children with pulmonary arterial hypertension: the PATENT–CHILD study. *Pulm Circ*. 2022;12:e12133. doi: 10.1002/pul2.12133
49. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, et al; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883–1893. doi: 10.1056/NEJMoa1915928
50. Efficacy, safety, and pharmacokinetics of vericiguat in pediatric participants with heart failure due to left ventricular systolic dysfunction (MK-1242-036). ClinicalTrials.gov identifier: NCT05714085. Updated October 1, 2024. Accessed October 11, 2024. https://www.clinicaltrials.gov/study/NCT05714085
51. Packer M, McMurray JJV, Krum H, Kiowski W, Massie BM, Caspi A, Pratt CM, Petrie MC, DeMets D, Kobrin I, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the ENABLE trials. *JACC Heart Fail*. 2017;5:317–326. doi: 10.1016/j.jchf.2017.02.021
52. Vachiéry J-L, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, Lack G, Papadakis K, Rubin LJ. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J*. 2018;51:1701886. doi: 10.1183/13993003.01886-2017
53. Kocabeyoglu SS, Kervan U, Sert DE, Karahan M, Kavurt AV, Koca S. Adaptation of adult right ventricular scoring systems to pediatric patients undergoing continuous LVAD implantation: feasible or not? *Int J Artif Organs*. 2023;46:280–288. doi: 10.1177/03913988231166731
54. Brancaccio G, Amodeo A, Ricci Z, Morelli S, Gagliardi MG, Iacobelli R, Michielon G, Picardo S, Parisi F, Pongiglione G, et al. Mechanical assist device as a bridge to heart transplantation in children less than 10 kilograms. *Ann Thorac Surg*. 2010;90:58–62. doi: 10.1016/j.athoracsur.2010.03.056
55. Schramm JE, Dykes JC, Hopper RK, Feinstein JA, Rosenthal DN, Kameny RJ. Pulmonary vasodilator therapy in pediatric patients on ventricular assist device support: a single-center experience and proposal for use. *ASAIO J*. 2023;69:1025–1030. doi: 10.1097/MAT.0000000000002023
56. Su JA, Menteer J. Outcomes of Berlin Heart EXCOR® pediatric ventricular assist device support in patients with restrictive and hypertrophic cardiomyopathy. *Pediatr Transplant*. 2017;21:e13048. doi: 10.1111/petr.13048
57. Lauder L, Bergmann MW, Paitazoglou C, Özdemir R, Iliadis C, Bartunek J, Lauten A, Keller T, Weber S, Sievert H, et al. Predicted impact of atrial flow regulator on survival in heart failure with reduced and preserved ejection fraction. *ESC Heart Fail*. 2023;10:2559–2566. doi: 10.1002/ehf2.14384
58. Paitazoglou C, Bergmann MW, Vrtovec B, Chamuleau SAJ, van Klarenbosch B, Wojakowski W, Michalewska-Włudarczyk A, Gyöngyösi M, Ekblond A, Haack-Sørensen M, et al. Rationale and design of the European multicentre study on Stem Cell Therapy in Ischemic Nontreatable Cardiac Disease (SCIENCE). *Eur J Heart Fail*. 2019;21:1032–1041. doi: 10.1002/ejhf.1412
59. Hansmann G, Sabiniewicz A, Sabiniewicz R. Atrial flow regulator for postcapillary pulmonary hypertension: first-in-human transcatheter AFR device implantations in RCM. *JACC Case Rep*. 2022;4:878–884. doi: 10.1016/j.jaccas.2022.05.010
60. Latus H, Apitz C, Schmidt D, Jux C, Mueller M, Bauer J, Akintuerk H, Schneider M, Schranz D. Potts shunt and atrial septostomy in pulmonary hypertension caused by left ventricular disease. *Ann Thorac Surg*. 2013;96:317–319. doi: 10.1016/j.athoracsur.2012.10.069
61. Bhat DP, Graziano JN, Garn BJ, Franklin WJ. Safety and utility of CardioMEMS device for remote pulmonary artery monitoring in paediatric Fontan patients: a case series. *Eur Heart J Case Rep*. 2023;7:ytad422. doi: 10.1093/ehjcr/ytad422
62. Hyotala K. Caring for pediatric heart failure patients with long-term mechanical circulatory support. *Crit Care Nurse*. 2018;38:44–56. doi: 10.4037/ccn2018313
63. Ubeda Tikkanen A, Berry E, LeCount E, Engstler K, Sager M, Esteso P. Rehabilitation in pediatric heart failure and heart transplant. *Front Pediatr*. 2021;9:674156. doi: 10.3389/fped.2021.674156
64. Velleca A, Shullo MA, Dhital K, Azeka E, Colvin M, DePasquale E, Farrero M, García-Guereta L, Jamero G, Khush K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2023;42:e1–e141. doi: 10.1016/j.healun.2022.10.015
65. Yeoh T-K, Frist WH, Lagerstrom C, Kasper EK, Groves J, Merrill W. Relationship of cardiac allograft size and pulmonary vascular resistance to long-term cardiopulmonary function. *J Heart Lung Transplant*. 1992;11:1168–1176.
66. Thangappan K, Zafar F, Ahmed HF, Greenberg JW, Ashfaq A, Hirsch R, Chin C, Lehenbauer D, O'Donnell A, Morales DLS. Is the practice of using oversized organs for recipients with elevated pulmonary vascular resistance justified? *J Thorac Cardiovasc Surg*. 2022;166:1766–1779. doi: 10.1016/j.jtcvs.2022.04.037
67. Singh TP, Cherikh WS, Hsich E, Chambers DC, Harhay MO, Hayes D, Khush KK, Perch M, Potena L, Sadavarte A, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-fourth pediatric heart transplantation report: 2021: focus on recipient characteristics. *J Heart Lung Transplant*. 2021;40:1050–1059. doi: 10.1016/j.healun.2021.07.022
68. Wu S, Hoang HB, Yang JZ, Papamatheakis DG, Poch DS, Alotaibi M, Lombardi S, Rodriguez C, Kim NH, Fernandes TM. Drug-drug interactions in the management of patients with pulmonary arterial hypertension. *Chest*. 2022;162:1360–1372. doi: 10.1016/j.chest.2022.06.042
69. Alyaydin E, Reinecke H, Tuleta I, Sindermann JR. Diltiazem as a cyclosporine A–sparing agent in heart transplantation: benefits beyond dose reduction. *Medicine (Baltimore)*. 2022;101:e31166. doi: 10.1097/MD.0000000000031166

Downloaded from http://ahajournals.org by on December 10, 2024

Circulation: Heart Failure