Overview of WHO Group 2 Pulmonary Hypertension Due to Left Heart Disease

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Van N. Selby, MD University of California, San Francisco Division of Cardiology San Francisco, CA **Background:** Left heart disease (LHD) is the most common cause of pulmonary hypertension (PH) and is associated with poor patient outcomes, especially among patients undergoing heart transplant evaluation.

Implications for clinicians: Left heart disease should be considered in all patients undergoing an evaluation for PH. Correct management of PH from LHD is to optimize treatment of LHD. Pulmonary vasodilators used to treat pulmonary arterial hypertension should not be used in patients with PH from LHD.

Conclusions: Additional research is needed to better understand how PH develops in patients with LHD and to investigate the role for treatment targeting PH in these patients.

as resulting only from passive trans-

mission of elevated left heart filling

pressures proximally into the pulmonary circulation vs increased pulmonary arte-

riolar resistance resulting from changes

in the function and structure of pul-

monary arterioles. The terms used to

describe patients in whom PH results

filling pressures include pulmonary

venous hypertension and passive PH.

The most recent guidelines recommend

using the term isolated postcapillary PH

(Ipc-PH) for this group of patients. In

filling pressures to normal also reduces

In other patients, the elevated mPAP

these patients, reduction of left heart

is not fully accounted for by passive,

proximal transmission of elevated left

heart filling pressures. In these patients,

it is believed that long-standing eleva-

vasoconstriction and remodeling of the

elevated out of proportion to the PAWP.

pulmonary arterioles so that mPAP is

Terms that have been used to describe

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this hemodynamic profile include mixed

tions in mPAP result in part from

mPAP to normal.^{1,11}

from transmission of elevated left heart

Left heart disease (LHD) is the most common cause of pulmonary hypertension (PH), and occurs in patients with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and valvular heart disease (Figure 1).^{1,2} The presence of PH in patients with LHD is associated with reduced exercise tolerance and reduced survival, especially following heart transplant.³⁻¹⁰ Identifying LHD as the cause of PH is critically important because it determines the correct approach to management, which is optimal treatment of the underlying LHD with evidence-based and/or standard-of-care pharmacologic or surgical therapies. In patients presenting with PH-LHD, there is currently no role for treatment with pulmonary arterial hypertension (PAH)-specific therapies and, with few exceptions, they should not be administered because they are costly, lack efficacy, and in some cases, are known to increase morbidity and mortality.

NOMENCLATURE, CLASSIFICATION, AND DEFINITIONS OF PH-LHD

The nomenclature that has emerged to categorize patients with PH-LHD attempts to describe the clinical context, pathophysiology, and hemodynamic features seen in these patients. This has resulted in a wide variety of terms used in an effort to accurately describe patients with PH-LHD. Multiple different terms, sometimes used in combination, may be appropriate to describe the unique characteristics of an individual patient with PH-LHD. Adding to this complexity is changes in terminology that have occurred over time as our understanding of PH-LHD has evolved. Recent guidelines attempted to simplify this language and to classify patients with PH-LHD according to hemodynamic characteristics (Table 1).

The hemodynamic definition of PH is a sustained elevation in mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. The usual hemodynamic findings in a patient with PH-LHD are mPAP \geq 25 mm Hg in combination with elevated left heart filling pressures, defined as a pulmonary artery wedge pressure (PAWP) >15 mm Hg or left ventricular end diastolic pressure (LVEDP) >15 mm Hg. The clinical characteristics (ie, presence of reduced ejection fraction [EF], clinical features of HFpEF, presence of valvular heart disease) are considered together with the hemodynamic features to arrive at a final diagnosis of PH-LHD.

In patients with PH-LHD, it is important to characterize elevated mPAP

recent guidelines recommend using the simple descriptive term "combined postcapillary and precapillary PH" (Cpc-PH). Differentiating Ipc-PH from Cpc-PH is important because it has prognostic implications, especially in patients undergoing evaluation for heart transplant (Figure 2). Typically, PH-LHD has been characterized by measures of resistance and pressure difference across the

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Figure 1: Causes of pulmonary hypertension due to left heart disease (PH-LHD).

pulmonary vasculature (Table 2). Patients have been considered to have Ipc-PH if the pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG) are normal and Cpc-PH if the PVR and TPG are elevated. Recent guidelines support the use of the diastolic pressure gradient (DPG) to differentiate the hemodynamic subtypes of PH-LHD.¹¹ The rationale for this recommendation is that the DPG is less dependent on stroke volume and left atrial pressure, and it was shown to be predictive of survival and correlated with pathologic changes.^{12,13} However, the DPG is subject to error^{14,15} and the association with survival is inconsistent, a reminder that a single measurement is rarely useful to characterize patients with PH.¹⁶⁻¹⁸

Vasodilator Testing

Further hemodynamic characterization of Cpc-PH is guideline-recommended in

patients with LHD-PH being considered for heart transplantation because it identifies patients at risk for posttransplant right ventricular (RV) failure and death.^{19,20} Vasodilator studies are conducted with a right heart catheter in place. A rapidly acting vasodilator is infused, typically nitroprusside, and measurements of the PVR and TPG are made.¹ Among patients in whom the PVR and TPG are reduced to normal levels while maintaining a systemic systolic blood pressure of \geq 85 mm Hg, PH is considered to be reversible or reactive. In these patients post-transplant mortality is similar to patients without PH.²¹ Among patients in whom PVR and TPG cannot be reduced to normal, PH is considered not acutely reversible. In many of these patients, the PVR may be lowered or become reversible after prolonged reduction of PAWP with aggressive treatment with diuretics, vasodilators, inodilators, and mechanical

Table 1. Nomenclature for Pulmonary Hypertension-Left Heart Disease.

Currently recommended terminology	Other commonly used terminology
Isolated postcapillary PH (Ipc-PH)	Pulmonary venous hypertension (PVH)
	Passive PH
Combined postcapillary and precapillary PH (Cpc-PH)	Mixed PH
	Out-of-proportion PH

PH = pulmonary hypertension.

support so that patients can become eligible for heart transplantation.

EPIDEMIOLOGY

Accurate prevalence estimates for PH-LHD are limited by factors such as reliance on echocardiographic assessments of pulmonary artery pressure (PAP) to identify affected patients,^{22,23} and inconsistent definitions and cutoffs to diagnose PH-LHD. Studies that make use of gold-standard invasive hemodynamics may be affected by referral bias since sicker patients are likely referred for right heart catheterization (RHC). Even well done invasive studies only provide data at a single time point while the patient is at rest, fasting, and possibly sedated—all of which may affect hemodynamic measurements.²⁴

Estimated rates of PH in LHD vary widely. The prevalence of Cpc-PH has ranged from 25% to 47% in hospitalized patients, and was 40% in a recent large ambulatory HFrEF population.^{10,25,26} Among patients with HFpEF, PH is present in 36% to 83%. A large community study examined echocardiograms from 244 patients with HFpEF and 719 hypertensive controls. Pulmonary hypertension, defined as pulmonary artery systolic pressure (PASP) > 35 mm Hg was found in83% of HFpEF patients compared to only 8% of controls. Using a higher PASP cutoff of 45 mm Hg would have resulted in prevalence of about 50%,^{7,27} a rate similar to that found in another study of 299 patients with HFpEF.²⁸ A single-center registry of patients undergoing RHC found PH, defined as PVR >2.5 or TPG >12, in 69% of HFpEF patients evaluated.29

Left-sided valvular heart disease is also commonly associated with PH and is important to recognize because it is an indication for valve replacement or repair. Mitral stenosis is the valvular lesion most often associated with PH, at a rate of up to 73%.³⁰ Pulmonary hypertension occurs at lower rates in patients with mitral regurgitation (23%–44%) and aortic stenosis (29%–47%).³¹⁻³⁷

PROGNOSIS

Compared to patients with LHD and no PH, patients with PH-LHD have



Figure 2: Classification and hemodynamic workup of PH-LHD. DPG = diastolic pulmonary gradient; LVEDP = left ventricular end-diastolic pressure; PADP = pulmonary artery diastolic pressure; PH = pulmonary hypertension; PAWP = pulmonary artery wedge pressure; RHC = right heart catheterization.

worse outcomes, including worse survival.^{4,27,38-41} This is true in both HFpEF and HFrEF and in studies using both echocardiography and invasive hemodynamics to diagnose PH.⁴¹ Additionally, survival worsens as PAP increases. A study of patients undergoing endomyocardial biopsy showed a 25% increase in the risk of death for every increase of 5 mm Hg in mPAP.⁴ Patients with Cpc-PH generally have more severe hemodynamic impairment and worse prognosis compared to Ipc-PH.^{4,10,26}

PATHOBIOLOGY AND PATHOPHYSIOLOGY

Our understanding of the pathophysiology of PH-LHD has improved in recent years; however, significant gaps remain. It is believed that the first event in the development of PH-LHD is increasing left heart filling pressures and pulmonary venous hypertension. Even when left ventricular (LV) systolic function is normal, diastolic filling abnormalities may result in increased PAP.⁴² Additionally, elevated left heart filling pressures also reduce compliance of the

Table 2. Hemodynamic Parameters Used in the Classification of Pulmonary Hypertension-Left Heart Disease.

Parameter	Calculation	Criteria for Cpc-PH
Transpulmonary gradient	mPAP - PAWP	>12
Pulmonary vascular resistance (PVR)	PVR/CO	>2.5-3.0 WU
Diastolic pulmonary gradient	PADP - PAWP	≥7 mm Hg

CO = cardiac output; PADP = pulmonary artery diastolic pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; WU = Wood units.

pulmonary vasculature and increase RV afterload by enhancing pulmonary artery wave reflections.43 Next, pulmonary arteriolar vasoconstriction occurs secondary to endothelial dysfunction characterized by decreased production of and/or decreased responsiveness to nitric oxide (NO), as well as overproduction of endothelin-1 (ET-1), activation of the reninangiotensin-aldosterone system (RAAS), and neurogenic activation. Elevated PAPs lead to injury, followed by pathologic remodeling of the pulmonary arterioles including muscularization, medial hypertrophy, and neointimal proliferation. 44-49 Ultimately the increased afterload imposed on the RV leads to RV systolic dysfunction and failure.3,50

ASSESSMENT AND DIAGNOSTIC APPROACH

Making a diagnosis of PH-LHD is challenging because symptoms are nonspecific, diagnostic tests can be difficult

Table 3. Assessment of Left Heart Disease in Pulmonary Hypertension.

Initial Tests	Contingent Tests	Favors Primary Contribution of LHD to PH	Favors Alternative Etiology of PH	
History	Targeted imaging and serologic evaluation	 Known left ventricular structural disease (eg, MI, cardiomyopathy) 	Conditions associated with WHO 1, 3–5 PAH (eg, family history of PAH, +BMPR2 mutation, HIV,	
		 Presence of comorbidities associated with LHD (eg, older age, diabetes, obesity, hypertension) 	 collagen vascular disease, hemoglobinopathy, portal hypertension, COPD, interstitial lung disease, appetite suppressant or other toxins, previous pulmonary embolism, congenital shunts) 	
		 Orthopnea and paroxysmal nocturnal dyspnea 		
Physical Exam		 Left-sided S3 or S4 gallop 	 Cyanosis, clubbing 	
		 Left-sided murmurs (particularly mitral) 	 Fine rales, protracted expiration, accessory muscle use, productive cough 	
		Displaced sustained apical impulse	 Raynaud phenomenon, sclerodactyly, telangiectasia 	
		• Coarse rales	Pulmonary vascular bruits	
			 Splenomegaly, spider angiomata, palmar erythema 	
Electrocardiogram	Exercise ECG	Q waves, left ventricular hypertrophy, left atrial enlargement, left bundle branch block, atrial fibrillation, inducible myocardial ischemia during exercise	Isolated right atrial enlargement and right ventricular hy pertrophy, S1Q3T3 pattern	
Echocardiogram (see Table 4)	Exercise echo	LV systolic dysfunction	 Isolated right atrial or right ventricular enlargement 	
Physical Exam Electrocardiogram (see Table 4) Right heart catheterization	Transesophageal echo	LV diastolic dysfunction	 Intraventricular septum flattening or reverse curvature 	
		LV hypertrophy	 Pericardial effusion in the absence of pericardial disease 	
		Mitral valve disease	 Congenital disease with shunt 	
		Cor triatriatum		
Right heart catheterization	Exercise	• PCWP or LVEDP > 15mm Hg	• PAP > 25 mm Hg with PCWP < 15 mm Hg	
	Vasodilator test	 Abrupt increase in PCWP (to >20–25 mm Hg) with exercise or volume loading 	• Exercise PCWP and LVEDP < 20–25 mm Hg	
	Volume loading	Increase PCWP noted during	-	
	Left heart catheterization	pulmonary-specific vasodilator testing		

BMPR = bone morphogenic protein receptor; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; HIV = human immunodeficiency virus; LV = left ventricular; LHD = left heart disease; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; S1Q3T3 = S wave in lead I, Q wave and T wave inversion in lead III; WHO = World Health Organization.

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to interpret, and PH may be multifactorial. Consequently, PH-LHD is often incorrectly diagnosed and treated as PAH, especially in elderly patients.^{51,52} A thoughtful and comprehensive approach to the evaluation of PH is needed so that appropriate treatment can be chosen.

History and Physical Examination

Information gathered during a comprehensive history and physical examination is important because it is used to prioritize next steps in the diagnostic evaluation and to provide context for the interpretation of diagnostic testing (Table 3). Details about congenital heart disease, murmurs, valvular disease, HFrEF and HFpEF, and coronary artery disease (CAD), as well as an assessment of risk factors for LHD should be ascertained. Special attention should be paid to factors associated with HFpEF²⁹ such as female gender, advanced age, diabetes, hypertension, Table 4. Distinguishing Pulmonary Hypertension-Left Heart Disease From Pulmonary Artery Hypertension Using Echocardiography.

		Likelihood of	
Echo Parameter	Echo Finding	PH-LHD	PAH
Ejection fraction	<50%	1	\downarrow
Left atrial size	LAD > 40 mm	↑	\downarrow
	$LAVI > 28 \text{ mm/m}^2$		
LV wall thickness	>11 mm	1	\downarrow
Transmitral Doppler	Grade II/III diastolic dysfunction	1	\downarrow
Mitral regurgitation	Severity $> 1 \times$	1	\downarrow
RV size	RV-to-LV area > 1.0	\downarrow	1
Interventricular septum	Systolic flattening	\downarrow	1
	Lateral-septal TDI disparity		
Interatrial septum	Bowing into LA	\downarrow	1
RV systolic function	TAPSE <1.5 cm	\downarrow	1
RVOT Doppler	Notching	\downarrow	↑

LAD = left atrial dimension; LAVI = left atrial volume index; LHD = left heart disease; LV = left ventricular; PH = pulmonary hypertension; RV = right ventricular; RVOT = right ventricular outflow; TDI = tissue Doppler imaging.

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CAD, arrhythmias, and sleep-disordered breathing. Orthopnea and paroxysmal nocturnal dyspnea in a patient with PH strongly suggest the presence of LHD. Physical examination findings that point toward LHD include pulmonary crackles, left-sided S3 or S4, left-sided murmurs, or irregular heart sounds consistent with arrhythmia.

Diagnostic Studies

An electrocardiogram and chest x-ray should be performed in all patients undergoing evaluation for PH. Though insensitive and nonspecific, these studies may point to LHD as a cause of PH with evidence of left heart disease such as evidence for myocardial infarction, abnormal heart rhythms, cardiac chamber enlargement or wall thickness, pulmonary edema or congestion, and the absence of parenchymal lung disease.

Echocardiography

Echocardiography is the most useful noninvasive modality for the evaluation of PH. It is easy to obtain and may immediately point to LHD as a cause of PH (Table 4, Figure 3). Echocardiographic findings of diastolic dysfunction are well described,⁵³ but are potentially insensitive for the diagnosis of HFpEF.^{27,54,55} Therefore, HFpEF should be suspected when findings such as LV hypertrophy and left atrial enlargement are present.²⁹ In a community-based study of 244 HFpEF patients and 719 hypertensive controls, elevated PAP on echocardiography was both sensitive and specific for the diagnosis of HFpEF,²⁷ suggesting that the presence of PH on echocardiography is often itself evidence of HFpEF.

Echocardiographic estimation of PASP is the most commonly used method to assess for PH. To estimate the PASP, the tricuspid regurgitant (TR) jet is imaged and interrogated with spectral Doppler in multiple echo windows, and the peak TR jet velocity is determined. The PASP is calculated using the modified Bernoulli equation: $PASP = 4(V^2) + right atrial (RA)$ pressure. This technique is limited because it cannot be utilized in patients without an adequate TR jet and spectral Doppler signal.⁹ Errors in estimation of PASP may lead to important misclassification of PH.²³

The shape of the ventricular outflow tract Doppler signal is useful to differentiate patents with PH-LHD. Transient flow deceleration in the right ventricular outflow tract during systole is caused by early return of reflected pulmonary arterial waves, resulting in notched pattern of the Doppler signal. Early wave reflection occurs in the setting of elevated PVR, and notching occurs earlier in systole as PVR increases. Thus, the presence of PH without notching strongly favors a diagnosis of PH-LHD, specifically Ipc-PH.⁵⁶

Echocardiography is also useful to assess for RV dysfunction, which is an important marker of increased mortality.^{3,57} Abnormalities of RV size, thickness, and function also provide evidence of clinically significant PH when the PASP cannot be estimated, or indicate that the severity of PH is worse than the estimated PASP suggests. Measurements including RV fractional area change, tricuspid annular systolic plane excursion (TAPSE), tissue Doppler imaging of the tricuspid valve annulus, and strain analysis may all be useful to assess RV systolic function and have prognostic value.57-59 These measurements have important limitations so that the overall impression of an experienced echocardiographer is important.

Magnetic Resonance Imaging

In patients with suspected PH-LHD, cardiac magnetic resonance imaging (CMR) is useful to detect structural abnormalities of the LV and left atrium, LV systolic function, presence of congenital heart disease, and presence of myocardial fibrosis or infiltrative disease. Similarly, RV enlargement, hypertrophy, and systolic function are best determined by CMR.

Right and Left Heart Catheterization

Data from an optimally performed RHC must be incorporated together with the patient's clinical characteristics and echocardiographic data to arrive at a final diagnosis of PH-LHD. In patients with PH-LHD, data from the RHC are also useful to optimize medical management and are necessary to assess risk in patients being considered for transplantation and mechanical circulatory support. It is crucial that the procedure be performed correctly and that data are properly collected and interpreted.^{60,61}



- Age >60 years
- Valvular heart disease
- Reduced LV ejection fraction
- Evidence of elevated LV pressures (LVH, diastolic dysfunction, LAE)
- Comorbidities supporting LV disease (DM, Htn, CAD, obesity)
- Markedly elevated BNP



Figure 3: Evaluation of PH identified by echocardiography. BNP = brain-type natriuretic peptide; CAD = coronary artery disease; DM = dia-betes mellitus; Htn = hypertension; LAE = left atrial enlargement; LHD = left heart disease; LVH = left ventricular hypertrophy; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension.

A complete hemodynamic assessment includes measurement of RA, RV, pulmonary artery and pulmonary artery wedge pressures, and cardiac output. All pressures should be determined at end expiration during spontaneous breathing to minimize the effects of intrathoracic pressure variation on the measurement. Thermodilution cardiac output when measured in triplicate and injected during end expiration⁶² remains valid even in the setting of low cardiac output and severe TR.⁶³

Incorrect determination of the PAWP may be secondary to many errors, including improper transducer position and zeroing to atmospheric pressure, waveform dampening, incompletely wedged catheter, placement in the RV, measurement that is not at end expiration, and use of the electronic mean obtained from the computer monitor. Mitral regurgitation causes large "v" waves that can be mistakenly interpreted as an elevated PAWP, confounding the calculation of the TPG and DPG. This can be accounted for by reading the PAWP at the time of the "a" wave. Several recent studies have examined the relationship between the PAWP and LVEDP and found that a substantial percentage of patients with PAWP \leq 15 had LVEDP >15, which could lead to misclassification of

patients with PH-LHD as PAH. Measurement of the LVEDP should be considered when a reliable PAWP tracing could not be obtained or the value of the PAWP is inconsistent with the expected value based on the clinical picture. Measurement performed manually on pressure tracings at end expiration is most tightly correlated with LVEDP.⁶⁴

Provocative Testing

Procedures in the catheterization laboratory are performed while patients are at rest in a fasting state and often after sedating medications have been administered. Hemodynamic findings of LHD

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may not be apparent under these conditions so that a diagnosis of LHD could be missed and patients are inappropriately diagnosed with PAH.65 To uncover hemodynamic abnormalities consistent with LHD, measurement of the PAWP after provocative testing with exercise or volume loading can be considered,⁶¹ especially in the setting of a clinical history or echocardiographic findings associated with HFpEF.⁶¹ In one recent report, after fluid challenge, 46 patients (22.2%) originally classified as having PAH were reclassified as having pulmonary venous hypertension, most secondary to LHD.66

MANAGEMENT OF PH-LHD

With few exceptions, the appropriate therapy for PH-LHD is optimizing treatment of the underlying LHD. In the case of HFrEF and HFpEF, therapy should include guideline-recommended treatments with diuretics, vasodilators, and neurohormonal antagonists, as well as with device and surgical therapies when appropriate.⁶⁷ The benefits of these therapies were emphasized in a recent study showing that adjustment of diuretics and vasodilator agents in response to data from continuous PAP monitoring devices reduced heart failure hospitalizations.68 Comorbidities that may contribute to PH such as sleep apnea, pulmonary embolism, and chronic obstructive pulmonary disease should also be identified and aggressively treated.

Increased morbidity and mortality associated with PH in patients with LHD makes PH an attractive therapeutic target. However, despite beneficial acute hemodynamic effects and small studies with phosphodiesterase type 5 (PDE5) inhibitors that have shown improvement in exercise capacity, no study has shown PAH therapies to be beneficial in PH-LHD, and some PAH therapies have been associated with significant adverse effects including increased mortality.^{1,8,69} Most studies of PAH therapies in LHD have not specifically enrolled PH-LHD, so it is possible that undetected benefits will be found in future trials.

Data demonstrating acute hemodynamic improvements including reduced PAWP, PVR, and increased cardiac output provided the rationale for the Flolan International Randomized Survival Trial (FIRST) of epoprostenol in HFrEF. However, the FIRST trial was stopped early when a trend toward increased mortality in the epoprostenol group was identified.⁷⁰ Multiple trials of endothelin receptor antagonists for the treatment of HFrEF have been performed and shown either no improvement or worsening edema and hospitalization. Several of these negative studies have never been published.⁷¹⁻⁷⁵

Phosphodiesterase type 5 inhibitors also have been shown to have beneficial acute hemodynamic benefits including improvements in gas exchange, skeletal muscle function, diastolic function, and RV function⁶⁹; reduced PVR and TPG; increasing cardiac output; improvements in peak oxygen consumption and 6-minute walk; and decreased heart failure hospitalizations.^{76,77} Similar improvements have been shown in patients treated with the soluble guanylate cyclase stimulator riociguat.78 In clinical practice, sildenafil also decreases PVR and improves RV function after heart transplantation and LVAD implantation.79,80 Despite these encouraging findings, long-term benefits of treatment with these agents have not yet been demonstrated in a randomized controlled trial so that they should not be routinely prescribed in patients with PH-LHD. Additional trials are now underway.

Prolonged treatment with intravenous vasodilators and mechanical support may restore vasodilator response in patients with HFrEF found to have initially irreversible Cpc-PH during heart transplant evaluation.⁸¹ In several reports, LV assist device support has been shown to be effective in reversing PH permitting heart transplant without increased rates of RV failure or death.^{79,82,83}

CONCLUSION

Much remains unknown about PH-LHD. An improved understanding of triggers and development of vascular changes in PH-LHD as well as the relationship between the LV and the pulmonary vasculature is needed. Failure of studies to demonstrate beneficial long-term outcomes in PH-LHD patients treated with pulmonary vasodilators suggests that PH in this setting may be a marker of severe or inadequately treated left heart failure. Studies that are specifically designed to focus on pulmonary vasodilators in PH-LHD patients with optimally managed LHD are needed.

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