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HEART FAILURE (HJ EISEN, SECTION EDITOR)

Pulmonary Hypertension Due to Left Heart Disease: an Update

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Abstract

Purpose of Review Pulmonary hypertension (PH) frequently complicates heart failure and portends a worse prognosis. This review will summarize and discuss recent updates in the classification and management of patients with PH due to left heart disease.

Recent Findings Careful hemodynamic assessment is critical to the classification of patients with PH and heart failure. Two hemodynamic subgroups of PH in heart failure patients have been described: isolated post-capillary pulmonary hypertension and combined post- and precapillary pulmonary hypertension. The cornerstone in management of PH due to left heart disease is the treatment of the underlying left heart pathology; however, ongoing trials have been designed to test pulmonary vasodilators in this cohort.

Summary PH-specific therapies have not demonstrated a benefit in patients with pulmonary hypertension due to left heart disease. Understanding the distinct pathobiology of each hemodynamic subgroup may lead to the development of useful biomarkers and effective targeted therapies.

Keywords Pulmonary hypertension · Heart failure · Left heart disease · WHO group 2 pulmonary hypertension · Post-capillary · HFpEF

Introduction

Pulmonary hypertension (PH) can occur due to numerous causes and is classified according to a system established by the World Health Organization (WHO). PH due to left heart disease (PH-LHD; WHO group 2) is encountered frequently in patients with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and valvular disease [1]. When present, PH-LHD typically is associated with worse exercise tolerance, higher symptom burden, and poor prognosis when compared with LHD patients without PH [2–4]. The presence of PH in patients with chronic HFrEF or HFpEF is associated with more symptoms, greater functional class impairment, and higher mortality [3–7]. Although PH-LHD is the most common etiology of PH worldwide, there remain limited proven therapies to reduce its associated morbidity or mortality.

The true prevalence of PH-LHD is unknown. Epidemiological studies have relied on echocardiography to estimate systolic pulmonary artery pressure; however, this method can both over- and underestimate true systolic pulmonary pressure [8, 9]. In a community-based cohort of patients with HFpEF, the prevalence of PH as determined by echocardiography was as high as 83% [4]. In a HFrEF cohort, Miller and colleagues found that 72% had a mean pulmonary artery pressure (mPAP) > 25 mmHg, and 35% had a pulmonary vascular resistance (PVR) ≥ 3 Wood units [10•]. PH is also common with left-sided valvular disease and increases in prevalence with valvular defects of greater severity. PH can be found virtually in all patients with severe symptomatic mitral valve disease and in up to 45% of those with severe aortic stenosis [11••, 12].

While targeted therapies continue to be developed for pulmonary arterial hypertension (PAH, WHO group 1) and chronic thromboembolic pulmonary hypertension (CTEPH, WHO group 4), these treatments have not been adequately studied and may be harmful in patients with PH-LHD. Thus,

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accurate diagnosis and classification remain critical. PH is particularly important for patients with severe heart failure being considered for heart transplantation, as it may adversely affect the allograft with associated high morbidity and mortality. This review summarizes the diagnosis of PH-LHD, highlights recent published data on management strategies, and proposes directions for further investigation.

Hemodynamic Diagnosis and Classification

Until recently, PH was defined hemodynamically by a sustained elevation of pulmonary arterial pressure, with elevated mPAP ≥ 25 mmHg measured by right heart catheterization at rest [1, 11•]. This definition is based on the examination of over 1100 healthy volunteers, which showed that mPAP under normal resting conditions ranges from 8 to 20 mmHg [13]. Although the clinical significance of mPAP between 21 and 24 mmHg remains unclear, it has been associated with worse outcomes in some analyses [14]. As a result, the 6th World Symposium on Pulmonary Hypertension task force on hemodynamic definitions and clinical classification proposed defining pulmonary hypertension as mPAP > 20 mmHg associated with a PVR ≥ 3 WU (Fig. 1) [16••]. The hemodynamic definition of PH-LHD or post-capillary pulmonary hypertension is a pulmonary arterial wedge pressure (PAWP) > 15 mmHg or left ventricular end-diastolic pressure (LVEDP) >18 mmHg (Table 1) [1, 11••, 17•]. A well-performed right heart catheterization with accurate and careful interpretation of measurements, especially with confirmation of left-sided filling pressures, is of paramount importance [18, 19].

Among patients with PH-LHD, two classes have been described: isolated post-capillary PH (Ipc-PH) and combined post-capillary and precapillary PH (Cpc-PH). In Ipc-PH, an elevation of PAWP leads to a proportional elevation in mPAP by a passive transmission of the high pulmonary venous and left atrial pressures [20, 21]. The Cpc-PH phenotype more closely resembles PAH [22, 23] and is characterized by chronic elevation of pulmonary venous pressures resulting in pulmonary arterial endothelial dysfunction, decreased nitric oxide availability, increased expression of endothelin-1, upregulation of neurohormones, and vascular remodeling [17•, 20, 22, 24].

The two forms of PH-LHD have been distinguished hemodynamically by the PVR, transpulmonary gradient (TPG = mPAP − PAWP), and the diastolic pulmonary artery pressure gradient (DPG), the difference between the diastolic pulmonary artery pressure (dPAP) and PAWP [17•, 25]. To date, Ipc-PH is defined as mPAP ≥ 25 mmHg, PAWP > 15 mmHg, TPG < 12 mmHg, DPG < 7 mmHg, and/or PVR ≤ 3 WU. On the other hand, Cpc-PH is defined by mPAP ≥ 25 mmHg, PAWP > 15 mmHg, DPG ≥ 7 mmHg, and/or PVR > 3 WU. Although Ipc-PH and Cpc-PH have been hemodynamically defined by the DPG, it remains unclear whether the DPG has useful

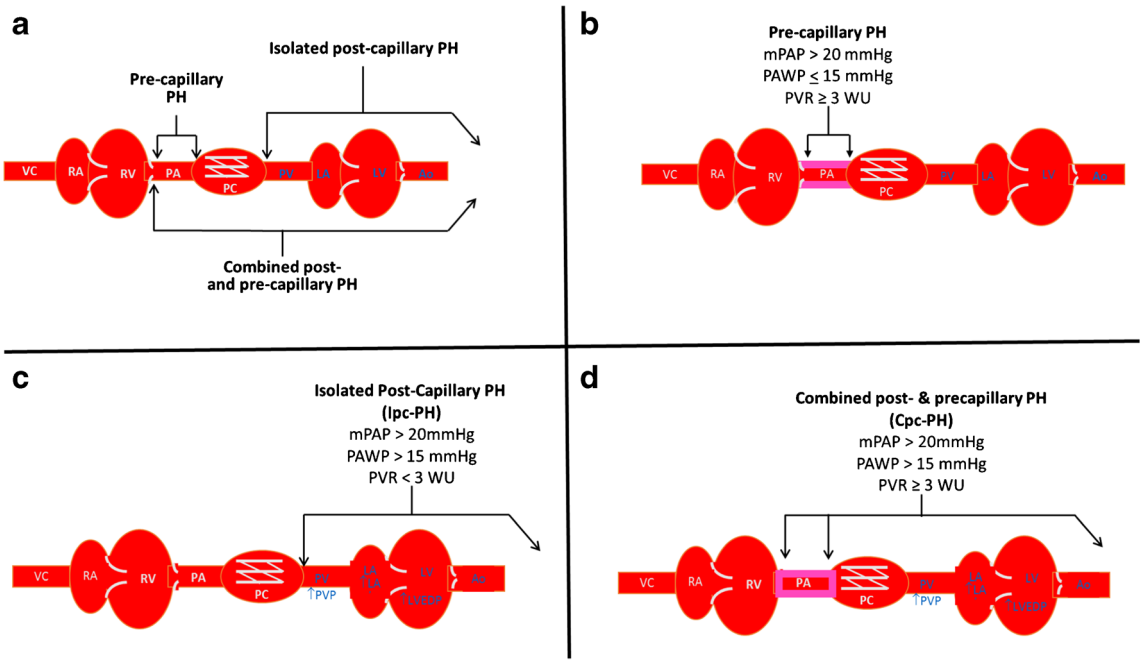

Fig. 1 **a** Overview of pulmonary hypertension hemodynamic profiles. **b** Precapillary pulmonary hypertension. **c** Isolated post-capillary pulmonary hypertension. **d** Combined post- and precapillary pulmonary hypertension. VC vena cava; RA right atrium; RV right ventricle; PA pulmonary arterial circulation; PC pulmonary capillary network; PV pulmonary venous circulation; LA left atrium; LV left ventricle; Ao aorta; PVR pulmonary vascular resistance; TPG transpulmonary gradient; DPG diastolic pulmonary gradient. (Adapted and modified from De Marco T et al., with permission from James K. Kirklin, Series Editor of *ISHLT Monograph Series, Volume 9: Pulmonary Hypertension and Right Heart Failure*) [15]

Table 1 Planned or actively recruiting/enrolling trials in PH due to HFpEF and HFrEF

Study	Intervention	Phase	Status	Population	Primary outcome
NCT03015402	Sodium nitrate	2	Recruiting	PH-HFpEF	mPAP during submaximal exercise
NCT03037580	Oral treprostinil	3	Recruiting	PH-HFpEF	Change in 6MWD
NCT02053246	Nebivolol	4	Recruiting	PH-HFpEF	Change in pulmonary vascular pressure
DYNAMIC, NCT02744339	Riociguat	2	Recruiting	PH-HFpEF	Change in cardiac output
SilHF-US, NCT03460470	Sildenafil	3	Recruiting	PH-HFrEF	Change in 6MWD
NCT02980068	Nitrates	1	Recruiting	PH-HFpEF	Change in nitrate level in urine and plasma; bacterial content of gut and oral microbiome
SPHERE-HF, NCT02775539	Mirabegron	2	Not yet recruiting	PH-HFrEF or PH-HFpEF	Change in PVR
NCT03541603	Levosimendan	2	Not yet recruiting	PH-HFpEF	Change in PCWP with bicycle exercise
NCT03629340	Metformin	2	Not yet recruiting	PH-HFpEF	mPAP during submaximal exercise
NCT01913847	Sildenafil	3	Recruiting	PH-HFrEF	Change in 6MWD
TROPHY-II, NCT03611270	Pulmonary denervation	n/a	Not yet recruiting	PH-HFrEF or PH-HFpEF	Procedural related adverse events
SERENADE, NCT03153111	Macitentan	2	Recruiting	PH-HFpEF	Change in NT-proBNP
SOPRANO, NCT02554903	Macitentan	2	Recruiting	PH following LVAD implantation	Change in PVR

Reference for all studies obtained on https://clinicaltrials.gov (accessed 10/29/2018)

mPAP, mean pulmonary artery pressure; 6MWD, 6-min walk distance; *PVR*, pulmonary vascular resistance; *LVAD*, left ventricular assist device

prognostic or clinical significance. It has been suggested that the DPG is less dependent on volume load and stroke volume than the TPG and less sensitive to changes in flow and filling pressures than the PVR. But whether DPG values predict outcomes in patients with PH-LHD remains controversial. While DPG was shown to be a predictor of survival in some retrospective PH-LHD studies [26–28], other retrospective analyses have failed to demonstrate a prognostic impact of the DPG in patients with PH and cardiomyopathy or heart transplant [29, 30]. The discrepant conclusions among these studies may be related to inconsistencies in measuring the PAWP. The mean PAWP (averaged throughout the cardiac cycle) in the presence of large v-waves will be higher than end-diastolic PAWP and may contribute to negative DPG values reported in many studies. In addition, the DPG values are affected by heart rate and may be discrepant in sepsis [30]. There is a movement to remove the DPG as a differentiating hemodynamic criterion for Ipc-PH and Cpc-PH. Both the PVR and TPG have commonly been used to identify a component of precapillary PH in LHD, and PVR has been shown to have better prognostic discrimination [10, 31]. Although it does not help differentiate Ipc-PH from Cpc-PH, pulmonary vascular compliance has been shown to be a stronger predictor of transplant-free survival than PVR or TPG [32, 33].

As a result of the limitations of the DPG and the better prognostic power of PVR, the 6th World Symposium on Pulmonary Hypertension proposed the following hemodynamic definitions in PH-LHD: [1] Ipc-PH, mPAP > 20 mmHg and PAWP > 15 mmHg and PVR < 3 WU; and [2] Cpc-PH, mPAP > 20 mmHg and PAWP > 15 mmHg and PVR ≥ 3WU ([34••]; Fig. 1).

While all the aforementioned variables have limitations to discriminate and prognosticate in PH-LHD, the most important hemodynamic parameter for the classification of patients is an accurately measured PAWP. Overestimation of left-sided filling pressures may prevent patients from receiving targeted therapy for WHO group 1 PAH, while underestimation of left-sided filling pressures may lead to inappropriate prescribing of pulmonary vasodilators. Despite its importance, the PAWP is inconsistently reported in the literature and is variably obtained in clinical practice. Catheterization should be performed in stable conditions with the transducer properly leveled at the mid-chest and "zeroed" to atmospheric pressure. Recordings should be measured during spontaneous breathing with patients positioned supine and head and legs flat. In the absence of mitral stenosis, PAWP measured at end diastole more closely approximates the LVEDP [35, 36]. The computer-obtained automated mean PAWP (averaged throughout the cardiac cycle) may be higher than end-diastolic PAWP, will overestimate the LVEDP, and may result in negative DPG values [35]. If PAWP is elevated or the accuracy is in question, one should obtain either a blood oxygen saturation in the wedge position (> 90% suggesting an accurate wedge position) or a left ventricular end-diastolic pressure via left heart catheterization (LVEDP > 18 mmHg indicating PH-LHD) [1].

The role of provocative testing (volume loading and exercise testing) to unmask PH-HFpEF is debated and under active investigation. Exercise-induced PH has traditionally

considered to be present when exercise mPAP ≥ 30 mmHg [1, 13, 37]; however, increases in mPAP and PAWP during exercise in middle-aged individuals may be normal [38]. Although a fluid challenge to diagnose HFpEF may be easier than exercise testing to standardize and execute, volume loading has similarly been shown to increase the PAWP in healthy volunteers [39]. Standardization of cutoff values for unmasking PH-LHD or HFpEF with provocative testing remains controversial.

Diagnostic Approach

Although the diagnosis of PH-LHD is defined hemodynamically, a right heart catheterization may not be sufficient to make a clear distinction between PAH and PH-LHD, especially when risk factors or comorbidities overlap [1, 11••, 17•]. Identifying LHD as the cause of PH is especially challenging in patients with HFpEF. Clues from the medical history favoring PH-LHD over PAH include older age, documented structural heart disease, exposure to cardiac toxins, or symptoms that are relatively specific to heart failure such as orthopnea or paroxysmal nocturnal dyspnea [1]. The presence of comorbidities such as obesity, hypertension, atrial fibrillation, diabetes, coronary artery disease, renal disease, and metabolic syndrome also increases the likelihood of HFpEF over PAH [1].

Echocardiography provides valuable data in the diagnosis of PH and can be used to help distinguish between PH-LHD and PAH. In patients with normal left ventricular dimensions and ejection fraction, echocardiographic parameters that suggest HFpEF include elevated tissue Doppler E/e′ ratio, short mitral E wave deceleration time, left atrial enlargement, a restrictive Doppler transmitral filling pattern, and LV hypertrophy [1, 20, 40]. An integrative score of five echocardiographic parameters (RV/LV ratio, left ventricular eccentricity index (LVEI), E/e′, RV forming apex, width and inspiratory collapse of IVC) as well as "notching" of the RV outflow tract Doppler envelope may be used to distinguish between precapillary from post-capillary PH [41, 42].

Identifying markers of high probability of PH-LHD from the medical history, physical exam findings, and echocardiogram can aid in establishing a pretest probability of PH-LHD and help incorporate findings from invasive testing. A risk score for HFpEF, integrating simple clinical characteristics and echocardiographic features, was recently described and used to discriminate from non-cardiac dyspnea [43]. Novel techniques in machine learning and unsupervised cluster analysis of echocardiographic data are being used detailed phenotypic analysis of cardiac structure and function in patients with HFpEF [44, 45]. Future studies in deep phenotyping in PH are likely to help in the non-invasive evaluation of PH-LHD.

Biomarkers

There is an unmet clinical need for biomarkers that distinguish between PH-LHD and PAH. Traditional circulating biomarkers such as B-type natriuretic peptide (BNP) and N-terminal fragment NT-proBNP are often elevated in PH, HFrEF, and HFpEF. BNP can be secreted from myocytes from both ventricles due to stretching in the setting of volume or pressure overload. Circulating BNP may be higher in Cpc-PH and Ipc-PH compared with PAH patients [22], but does not discriminate well between WHO group 1 and 2 diseases [20]. Additionally, natriuretic peptides are not consistently reliable as they may be disproportionately elevated in the elderly or in patients with renal failure and falsely reduced in obese patients.

The suppression of tumorigenicity 2 receptor is a member of the interleukin-1 family of receptors and exists as a transmembrane and soluble isoform. Soluble suppression of tumorigenicity 2 receptor (sST2) is a biomarker that is elevated in some systemic inflammatory diseases. In experimental cardiac models, mechanical stress of cardiomyocytes and neurohormonal activation leads to activation of the ST2 signaling. Elevated levels of sST2 have been repeatedly shown to be associated with worse outcomes in HFrEF. Serial testing for sST2 increases the prognostic information gained compared with single measurement and predicts worsening left ventricular remodeling, risk for hospitalization, and heart failure death [46, 47]. Circulating sST2 is associated with proinflammatory comorbidities and right ventricular pressure overload and dysfunction in a HFpEF cohort [48]. Other data in a hypertensive heart failure cohort showed a significant correlation between soluble ST2 and right ventricular systolic pressure, right ventricular dimensions, and right atrial area [49]. Thus, sST2 may have a diagnostic and prognostic value in early detection of PH-LHD and right ventricular dysfunction in heart failure cohorts.

Metabolomics has emerged as a powerful tool for defining disturbances in cardiac metabolism that occurs across a spectrum of disease states [50]. Targeted metabolic profiling of patients with PH revealed changes in 21 metabolites that were associated with indices of right ventricular function or pulmonary vascular resistance. Among these, circulating indoleamine 2,3-dioxygenase–dependent tryptophan metabolites (IDO-TMs) inversely correlated with RV function, directly correlated with PVR, and were able to identify patients with right ventricular dysfunction from a high-risk cohort [51]. Profiling metabolites in the RELAX clinical trial showed higher baseline levels of short-chain dicarboxylacylcarnitine metabolites, and asparagine/aspartic acid was associated with worse clinical rank scores in HFpEF patients treated with sildenafil or placebo. Additionally, increases in long-chain acylcarnitine metabolites and short-chain dicarboxylacylcarnitines in the HFpEF group treated with sildenafil correlated with increases in endothelin-

1 and creatinine/cystatin C, respectively [52]. However, in a cohort of PH patients referred for catheterization, Luo and colleagues found that long-chain acylcarnitines were higher in all PH cases versus in non-PH controls, but did not discriminate between Cpc-PH and Ipc-PH [53]. While circulating metabolites may offer insights into biochemical pathways involved in the failing heart, additional work is needed in the development and validation of these circulating factors to be useful as biomarkers.

New Insights into Management of PH-LHD

The goal of therapy for PH-LHD is to alleviate symptoms, improve exercise tolerance, preserve right ventricular function, and ultimately reduce morbidity and mortality. First-line therapy for PH-LHD continues to be the optimization of treatment for underlying LHD [11••]. This often involves adjusting vasodilators, diuretics, and neurohormonal antagonists for HFrEF. In subgroup analysis, spironolactone appears to reduce hospitalizations for patients with HFpEF and may improve survival [54, 55]. Comorbidities that contribute to PH-LHD such as atrial fibrillation, sleep apnea, and systemic hypertension should also be identified and aggressively treated, particularly for HFpEF where few other targeted therapies exist.

Structural left heart disease should be corrected when possible. The presence of PH in valvular disease results from remodeling of the pulmonary circuit from chronically elevated pulmonary venous pressure and correlates with the severity of the underlying valvular abnormality. When valvular disease is the cause of PH-LHD, correction often leads to substantial improvements in pulmonary pressures and PVR [56]. Surgical correction of mitral valve disease in patients with systolic PA pressures > 50 mmHg resulted in a substantial decrease in left atrial pressure and PVR [57]. A more recent retrospective analysis of 654 patients with degenerative mitral regurgitation with or without PH found similar short-term (30-day) and long-term (10-year) survival rates. The incidence of late cardiac events was not different between the two, but the recurrence of PH was more frequent in those with PH [58]. Data from catheter-based interventions for mitral valve disease are lacking, but further analyses of pulmonary hypertension from cohorts undergoing percutaneous mitral valve repair of functional mitral regurgitation are forthcoming [59, 60].

Pulmonary hypertension is highly prevalent in aortic stenosis. A multicenter retrospective registry of consecutive patients undergoing transcatheter aortic valve implantation (TAVI) found that 47% patients had systolic PA pressure ≥ 40 mmHg on echocardiogram, which was associated with higher all-cause mortality [61]. Similarly, a prospective, observational study from the Mayo Clinic showed that presence in the highest PA systolic pressure tertile (PASP ≥ 49 mmHg) prior to undergoing TAVI was an independent predictor of long-term mortality. TAVI was associated with a decrease in PA systolic pressure in the highest tertile at 1 week after the procedure [62].

In some cases, correcting the underlying valvular disease does not resolve the pulmonary hypertension. The Sildenafil for improving Outcomes after Valvular Correction study (SIOVAC) aimed to determine whether treating persistent pulmonary hypertension after successful valve replacement or repair, with sildenafil, improved outcomes. The multicenter randomized clinical trial enrolled patients with persistent pulmonary hypertension (mPAP ≥ 30 mmHg) who had undergone valve procedure at least 1 year prior to inclusion. Patients were randomized to sildenafil 40 mg three times a day or placebo for 6 months. Treatment with sildenafil in this cohort led to worsening of the primary composite endpoint of death, hospitalization for heart failure, or change in functional class and patient global assessment [63]. Importantly, patients in both groups had persistently elevated PAWP (mean PAWP 23 mmHg in the sildenafil group and 22 mmHg in the placebo group) with low DPG (2.0 in the sildenafil group and 3.0 in the placebo group) and mildly elevated PVR (3.4 WU in the sildenafil group and 3.1 WU in the placebo group). Therefore, for patients with PH-LHD and persistently elevated PAWP, sildenafil should not be recommended, while the potential for alternative therapies remains undetermined.

Use of pulmonary vasodilators in the treatment of PH due to chronic HFrEF or HFpEF is an attractive strategy given the likely overlap in disease processes. Indeed, in both HFrEF and HFpEF, PH is associated with global pulmonary vascular remodeling [64]. However, randomized clinical trials in chronic HFrEF, and recently in HFpEF, have not shown an improvement in clinically relevant outcomes. This rationale prompted the Flolan International Randomized Survival Trial (FIRST) of epoprostenol in HFrEF which demonstrated acute hemodynamic improvements including reduced PAWP, PVR, and increased cardiac output with epoprosenol therapy. However, the trial was stopped early due to a trend toward increased mortality in the epoprostenol group [65]. Multiple trials of endothelin receptor antagonists for the treatment of HFrEF have shown either no improvement or worsening volume overload and hospitalization. The ENABLE trial found that bosentan led to early and clinically important fluid retention in patients with New York Heart Association (NYHA) class IIIb/IV chronic HFrEF [66]. The MELODY-1 study studied the effect of macitentan therapy on fluid retention and functional class in patients with heart failure patients (LVEF ≥ 30%, NYHA class II or III) and Cpc-PH (DPG ≥ 7 mmHg and PVR > 3 WU). In the study population where the majority of patients had HFpEF (76% had EF ≥ 50%), the authors found a statistically significant greater proportion of patients in the macitentan group suffered significant fluid retention, worsening NYHA class symptoms, and at least one adverse effect. Together, these studies suggest that endothelin receptor antagonists should not be used in patients with HFrEF or HFpEF.

Pulmonary vasodilation can also be achieved by increasing smooth muscle cyclic guanosine monophosphate (cGMP) with phosphodiesterase-5 (PDE-5) inhibition. PDE-5 inhibition has been shown to have beneficial acute hemodynamic benefits including improvements in gas exchange, skeletal muscle function, diastolic function, and RV systolic function which may be beneficial in heart failure patients [67]. In HFrEF patients with elevated PVR, sildenafil restores the impaired transpulmonary release of cGMP without an impact on PAWP [68]. The Phosphodiesterase Type 5 Inhibition with Tadalafil Changes Outcomes in Heart Failure (PITCH-HF) trial was powered for cardiovascular mortality and heart failure hospitalizations but was unfortunately suspended due to missing enrollment milestones (see clinicaltrials.gov NCT01910389). The SilHF trial is a randomized, placebo-controlled multinational trial that will investigate whether sildenafil can improve exercise capacity and symptoms in NYHA class II–III heart failure patients with HFrEF and PH (Table 1) [67]. Although a benefit of sildenafil in HFpEF was suggested in a single-center study of HFpEF patients with PH [69], sildenafil did not improve RV function, exercise capacitance, or ventilator efficiency in a multicenter HFpEF trial [70], nor did it improve these measurements in patients with HFpEF and RV dysfunction [71].

Nitric oxide produces vasodilation by stimulating soluble guanylate cyclase (sGC) and thereby increasing cGMP levels in a distinct manner from PDE-5 inhibitors. Riociguat, a nitric oxide–independent sGC stimulator, was shown to improve cardiac and stroke volume indices, but not mPAP in a randomized, placebo-controlled trial of 201 patients with HFrEF and PH. Riociguat was also tested in PH-LHD due to HFpEF. In the DILATE-1 trial, HFpEF patients with mPAP ≥ 25 mmHg and PAWP > 15 mmHg were randomized to single oral doses of 0.5, 1, or 2 mg riociguat or placebo. The authors found no significant difference in the peak decrease in mPAP with riociguat or placebo. However, riociguat increased stroke volume and decreased systolic blood pressure and right ventricular end-diastolic area [72]. The SOCRATES program assessed the role of another sGC stimulator, i.e., vericiguat, in HFrEF as measured by changes in biomarkers (SOCRATES-REDUCED [73]) and HFpEF (SOCRATES-PRESERVED [74]). In SOCRATES-REDUCED, vericiguat did not have a statistically significant effect on NT-proBNP levels in 12 weeks, while in SOCRATES-PRESERVED, vericiguat did not change NT-proBNP or left atrial volume in 12 weeks. Given the inconsistent data on surrogate endpoints, sGC are now being investigated for outcomes in HFrEF and HFpEF. The VICTORIA trial is an ongoing randomized, double-blind, placebo-controlled trial investigating the effect of vericiguat on outcomes of cardiovascular death and heart failure hospitalizations in patients with HFrEF (clinicaltrials.gov NCT02861534) [75]. The VITALITY-HFpEF trial is a randomized, parallel-group, placebo-controlled, double-blind trial that will investigate the effect of vericiguat in functional status and 6-min walk distance in patients with HFpEF (clinicaltrials.gov NCT03547583). In addition to investigating medications to improve outcomes in PH-LHD, novel procedural-based approaches such as pulmonary artery denervation using radiofrequency catheter ablation (clinicaltrials.gov NCT 02220335) are also being investigated (Table 1).

Patients undergoing heart transplant with Cpc-PH risk higher early mortality, right heart failure, and worse transplant survival [76•, 77]. For these reasons, it is important to obtain right heart catheterization in all heart transplant candidates before listing, and in 3- to 6-month intervals while awaiting transplantation, especially in the setting of PH or worsening heart failure [78]. An acute vasodilator challenge should be performed in heart transplant candidates if the systolic PA pressure > 50 mmHg, and either the TPG > 15 mmHg or PVR > 3 Woods units while maintaining a systemic systolic arterial pressure > 85 mmHg (Fig. 1) [78]. When the acute vasodilator challenge is unsuccessful at obtaining hemodynamics suitable for transplant, also referred as "irreversible/persistent" PH, the combination of medical therapy and mechanical unloading of the left ventricle may be necessary to achieve acceptable pulmonary hemodynamics. Mechanical circulatory support with a left ventricular assist device (LVAD) is consistently able to reduce pulmonary pressures, even in many cases where the PH was believed to be acutely irreversible [79–82]. Implantation of a LVAD unloads the left ventricle and reduces pulmonary pressures and PVR in heart transplant candidates with PH that was deemed irreversible on acute vasodilator testing [83], with survival outcomes similar to those without PH [79]. This mechanical unloading is thought to favorably promote pulmonary vascular remodeling and in turn, reduce PA pressures over weeks to months and permit heart transplant without increased rates of RV failure or death. Persistent pulmonary vascular and left ventricular pressure decoupling in spite of LVAD therapy is associated with worse prognosis compared with those who improve [84]. Outside of this setting, acute vasoreactivity testing does not predict outcomes in PH-LHD [11, 17, 85].

Clinical trials are necessary to understand the optimal combination of WHO group 1 PH medical therapies and mechanical unloading in patients with Cpc-PH being optimized for heart transplantation. Concomitant use of PDE-5 inhibitors, in particular sildenafil, has been suggested to be effective in this cohort of patients [86•]. In the perioperative setting, sildenafil improves pulmonary hemodynamics and significantly increases cardiac output [87]. More than 40% of the patients in a study by Tedford and colleagues had reduced PVR < 3–3.5 Wood units with the combination of LVAD and sildenafil therapy, allowing them to become heart transplant candidates [86•]. Despite these encouraging findings, long-term benefits of treatment with these agents have not yet been demonstrated in randomized controlled trials. Studies are also under way to explore the use of endothelin receptor antagonists in patients with preexisting PH-LHD and subsequently normalized PCWP, as is the case post-LVAD or

post-heart transplant. One such study will examine the efficacy and safety of macitentan in patients with persistent PH after LVAD implant (SOPRANO, clinicaltrials.gov; Table 1). Thus, the combination of mechanical unloading with medical therapy potentially holds promise in the treatment of advanced heart failure patients with Cpc-PH.

Conclusion

The presence of PH increases morbidity and mortality for patients with heart failure. What may start as passive pulmonary venous hypertension may cause vascular remodeling and pulmonary arterial endothelial dysfunction. The entity of Cpc-PH is common in left heart disease and adversely impacts clinical outcomes above and beyond Ipc-PH. Basic and translational research efforts focused on Cpc-PH are needed to better our understanding of its pathophysiology and disease progression, identify risk factors, and develop non-hemodynamic biomarkers for diagnosis and prognosis. The clinical experience with LVADs reminds us of the classic teaching of PH-LHD, which is to treat the underlying left heart disease in PH-LHD and reduce elevated left ventricular filling pressures. Additional randomized clinical trials are needed to determine which combination of medical and mechanical unloading provides the best immediate and long-term outcome for these patients.

Compliance with Ethical Standards

Conflict of Interest Mandar A. Aras reports no conflict of interest.

Mitchell A. Psotka reports being a consultant for Roivant, Amgen, and Cytokinetics.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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