Current Treatment Strategies in Pulmonary Hypertension Associated with Left Heart Disease

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Abstract Pulmonary hypertension (PH) is a common complication of left heart disease (LHD) and is associated with impaired functional capacity and decreased survival. Recent guidelines have proposed a new classification system for PH-LHD that is based on the diastolic pulmonary gradient. Despite a sound physiologic basis, subsequent studies have not found a significant correlation between the diastolic pulmonary gradient and meaningful outcomes. Treatment of PH-LHD focuses on optimizing the left heart disease. The use of medications for the treatment of combined post- and pre-capillary PH in left heart disease is controversial. While several small studies have shown hemodynamic or symptomatic improvement, none have been demonstrated to clearly improve long-term outcomes. Large, event-driven trials of PH-LHD are needed to guide the optimal management of this population.

Keywords Pulmonary hypertension · Heart failure · Diastolic pulmonary gradient · Heart transplant

Introduction

Pulmonary hypertension (PH) is a frequent complication of left heart disease (LHD). It is most commonly seen in patients with heart failure (HF), and its presence is associated with

more severe symptoms, reduced functional capacity, and reduced survival [1•, 2, 3]. Pulmonary hypertension associated with LHD is initially caused by passive transmission of elevated left-sided filling pressures. With long-standing pulmonary venous hypertension (post-capillary PH) associated with neurohormonal and other mediator upregulation and neurogenic stimuli, some patients will develop pulmonary vasoconstriction with or without vascular remodeling [4]. Identifying post-capillary PH with a significant pre-capillary component (combined post- and pre-capillary PH; Cpc-PH) is crucial for multiple reasons, including establishing heart transplant candidacy [5] and need for intervening circulatory support at a bridge to transplant.

For those with substantial pre-capillary disease despite maximal treatment of the LHD, there is growing interest in the application of pulmonary arterial hypertension (PAH)-specific therapies for PH-LHD. Although promising, this practice is not currently supported by evidence from large, prospective, well-conducted clinical trials. This review will address the epidemiology, current definitions, and therapeutic options for PH-LHD.

Epidemiology

Prevalence

The true prevalence of PH-LHD is unknown, with estimates ranging from 25 to 83 % [6–8]. This uncertainty is related to several factors including variations in the definition of PH-LHD used in the literature, heterogeneity of the populations studied, and data that are derived from either large community-based cohorts or tertiary care centers [3, 8, 9]. Many studies have used data based solely on echocardiographic measurements of systolic pulmonary artery pressure

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(sPAP) [6–8]. Estimates of prevalence based on invasive hemodynamics have been published [10], but such studies may be subject to referral bias as sicker patients are more likely to be referred for right heart catheterization (RHC). Regardless of the exact prevalence, PH-LHD is the most common type of PH encountered in clinical practice [10, 11].

PH-LHD is seen in all of the commonly encountered forms of LHD. In a cohort of 244 patients with heart failure and preserved ejection fraction (HFpEF), Lam et al. found that 83 % had PH compared to just 8 % in a control sample of hypertensive patients without HF [8]. Pulmonary hypertension is similarly common among patients with heart failure and reduced ejection fraction (HFrEF). In a study of 1541 patients with LV ejection fraction (EF) <40 %, Miller and colleagues found that 72 % had a mean PA pressure (mPAP) >25 mmHg and 35 % had a pulmonary vascular resistance (PVR) ≥ 3 Wood units (Wu) [12]. Pulmonary hypertension is also a common complication of valvular heart disease, with mitral stenosis the most strongly associated. Hart and colleagues found that 73 % of patients with mitral stenosis had mPAP ≥ 25 mmHg [13]. Pulmonary hypertension is common in patients with other forms of valvular LHD, though less so compared to mitral stenosis. In a study of 1080 patients with severe aortic stenosis referred for AVR, PH was identified in 47 % [14]. In a large multicenter registry of patients with significant mitral regurgitation 23 % of the patients had sPAP >50 mmHg [15].

Prognostic Implications

The association between PH and worse prognosis in patients with LHD is well established. In a cohort of patients referred for endomyocardial biopsy, Cappola and colleagues found that every 5 mmHg increase in the mPAP was associated with a 25 % increase in the risk of death [16]. Among patients with PH-LHD, those with significant pre-capillary disease (Cpc-PH) generally have worse hemodynamics and prognosis. PVR has been a particularly strong predictor of outcomes [16, 17].

Diagnostic Approach and Classification of PH-LHD

Pulmonary hypertension is defined as sustained elevation of the mean PA pressure of ≥ 25 mmHg at rest, as measured by RHC. Pulmonary hypertension can occur due to a variety of causes and is generally categorized according to the system established by the World Health Organization [18]. Pulmonary hypertension due to left heart disease (WHO group 2) is characterized by elevated left-sided filling pressure, most commonly defined as a pulmonary artery wedge pressure (PAWP) >15 mmHg. The left atrial pressure or left ventricular end-diastolic pressure (LVEDP) may be used as appropriate and available, especially if the PAWP accuracy needs

confirmation in the absence of mitral valve disease. The importance of a well-performed RHC and careful interpretation of measurements, specifically confirmation of the left-sided filling pressure, cannot be overemphasized [19]. It is imperative to level the transducer at atrial level and to zero to atmospheric pressure. The standard is to measure pressures at end-expiration. Accuracy of the PAWP can be confirmed by measuring oxygen saturation from a sample drawn in the wedge position showing a peripheral capillary oxygen saturation (SpO₂) >90 %. If the SpO₂ is <90, then direct left heart pressures should be measured (left ventricular end-diastolic pressure, rarely left atrial pressure). While there are no formal guidelines for right heart catheterization, expert recommendations are available [20]. Data from a well-performed RHC must be incorporated with each patient's clinical presentation and echocardiographic findings to clearly differentiate PH-LHD from PAH or other causes of pulmonary hypertension. One of the most challenging determinations encountered in the hemodynamic assessment of PH is differentiating PAH from PH-HFpEF. Echocardiography is often used as an initial diagnostic test, and an LV EF <50 % favors PH-LHD. In patients with normal EF, no single echocardiographic finding is specific for PH-LHD. Doppler evidence of diastolic dysfunction can be seen in both PH-LHD and pulmonary vascular disease [21], though more dramatic measures of LV diastolic dysfunction such as elevated tissue-Doppler E/e' ratio, a restrictive transmitral filling pattern, and left atrial enlargement all favor PH-LHD [22–24]. Echocardiography can also be used to estimate PVR. Systolic notching of the RV outflow tract Doppler flow velocity envelope, created by early wave reflection due to stiff pulmonary vasculature, was highly associated with PVR >3 Wu in one cohort of subjects with PH [25]. Invasive hemodynamic assessment remains the gold standard for differentiating PH-LHD from PAH. Both volume loading and exercise at the time of RHC have been suggested, though recent evidence suggests exercise may be more sensitive for unmasking hemodynamic abnormalities suggestive of HFpEF [26].

Vasodilator Testing

In patients with Cpc-PH, vasodilator testing is used to differentiate those with reversible pre-capillary PH from those with fixed disease due to pulmonary vascular remodeling. Vasodilator testing is particularly useful in patients undergoing evaluation for heart transplantation to avoid acute donor right heart failure at the time of transplantation which is associated with high mortality up to 3 months post transplant [27]. Patients with Cpc-PH in whom the pre-capillary component (assessed using the transpulmonary gradient (TPG) or PVR) can be effectively reduced with vasodilators have similar post-transplant mortality compared to patients with PH [28, 29]. Current guidelines recommend vasodilator testing in all heart

transplant candidates when sPAP ≥ 50 mmHg and either TPG ≥ 15 mmHg or PVR > 3 Wu [5].

Because of the possibility of hemodynamic instability, short-acting vasodilator agents are generally preferred for diagnostic testing. Protocols using nitroprusside, milrinone, prostacyclins, nitric oxide, and nitroglycerin have all been reported [27, 30–32]. After obtaining resting hemodynamics, the vasodilator is initiated and the dose is up-titrated incrementally with regular hemodynamic measurements and close monitoring for the development of hypotension (systolic blood pressure (SBP) < 90 mmHg) or other evidence of hypoperfusion. Ability to achieve a PVR < 2.5 Wu while maintaining adequate systemic blood pressure (SBP > 85 mmHg) identifies patients at lower risk of post-transplant mortality [27]. Close monitoring during titration of vasodilator agents is critical given the potential for adverse effects. By decreasing the pulmonary vascular resistance and increasing transpulmonary blood flow, IV prostacyclins and inhaled nitric oxide may cause an acute increase in the PAWP and precipitate pulmonary edema [33]. For these reasons, nitroprusside is generally the preferred agent for evaluation of reversibility in PH-LHD [1••].

Definitions of PH-LHD

Classification of PH-LHD primarily distinguishes patients with PH stemming from elevated left-sided pressures from those with underlying primary pulmonary vascular disease. The distinction has historically been made based on the TPG (mPAP-PAWP) or the PVR. Patients with high TPG or PVR have significant pre-capillary disease and have traditionally been referred to as “out of proportion,” “reactive,” or “mixed” PH. Most studies have found the development of pre-capillary disease to be associated with a worse prognosis [12, 16]. Identification of PH-LHD patients with significant pre-capillary disease becomes particularly important during consideration of heart transplantation. The extent of pulmonary vascular disease is directly correlated to post-transplant survival in this population [34].

A recent PH-LHD consensus paper identified several flaws in the current definition and classification of PH-LHD, including marked heterogeneity and confusion with the terminology used to describe PAH [35••]. Furthermore, the consensus panel identified physiologic shortcomings of the TPG. The TPG fluctuates with changes in both stroke volume and left atrial pressure [36, 37]. The diastolic pulmonary gradient (DPG; PA diastolic pressure-PAWP) on the other hand is less dependent on these factors. In an initial study Gerges et al. found that DPG was strongly associated with survival and pathologic changes in PH-LHD [38•].

Based on these findings, the World Symposium on Pulmonary Hypertension task force on PH and LHD proposed a new classification and definition for PH-LHD. Those with significant

pre-capillary disease as defined by DPG > 7 mmHg and PAWP > 15 mmHg are referred to as “combined post-capillary and pre-capillary PH (Cpc-PH),” while those with PAWP > 15 mmHg but DPG < 7 mmHg are referred to as “isolated post-capillary PH (Ipc-PH)” (Fig. 1). Although DPG is based on sound physiologic evidence and promising initial findings, several potential pitfalls related to the DPG have been identified. The diastolic PA pressure is especially prone to factors such as catheter whip [39], and inaccurate measurements related to use of computer-generated measurements or failure to obtain measurements at end-expiration could have particularly dramatic effects on the DPG. Factors such as heart rate [40], hypoxia [41], and sepsis [42] have also been shown to impact the DPG. In subsequent studies the DPG has not been a strong predictor of survival in PH-LHD including patients undergoing right heart catheterization for evaluation of unexplained cardiomyopathy [43], heart transplant patients [44], and patients referred for left ventricular assist device (LVAD) implantation [45]. The concept of a purely DPG-based definition of PH-LHD requires further evaluation and validation before widespread adoption can be recommended.

Treatment of PH-LHD

Goals of therapy in PH-LHD include alleviating patient symptoms, increasing exercise capacity, preventing right ventricular dysfunction, delaying disease progression, and ultimately reducing morbidity and mortality. The primary treatment of PH-LHD is management of the underlying condition [11]. Most often, this involves medical therapy for chronic HF including vasodilators, diuretics, and neurohormonal antagonists.

Repair of Valvular Heart Disease

When valvular heart disease is the cause of PH-LHD, correction often leads to substantial improvements in PA pressure and or PVR. Mitral valve disease, for example, is associated with elevated left atrial pressure that frequently leads to Cpc-PH. One series reported severe PH (PVR > 6 Wu) in 26 % of patients with mitral stenosis [46], and PH is commonly seen in mitral regurgitation as well. In a study of 31 patients with mitral valve disease and sPAP > 50 mmHg, surgical correction resulted in a substantial decrease in left atrial pressure and PVR [47].

Pulmonary hypertension is also seen in approximately 30 % of patients with severe aortic stenosis (AS) [48]. A retrospective study of 47 patients with severe AS and severe PH (peak tricuspid regurgitation velocity ≥ 4 m/s by echocardiography) found 80 % mortality in those treated conservatively. Among patients treated with aortic valve replacement,

Fig. 1 **a** Pulmonary hypertension hemodynamic profiles. **b** Pre-capillary PH. **c** Isolated post-capillary or passive PH. **d** Combined post- and pre-capillary or mixed PH. *AO* aorta, *BNP* B-type natriuretic peptide, *DPG* diastolic pulmonary gradient (diastolic pulmonary artery–pulmonary arterial wedge pressure), *ET-1* endothelin-1, *LA* left atrium, *LAP* left atrial pressure, *LV* left ventricle, *LVEDP* left ventricular end-diastolic pressure, *NO* nitric oxide, *PA* pulmonary arterial circulation, *PC* pulmonary

capillary network, *PAWP* pulmonary arterial wedge pressure, *PH* pulmonary hypertension, *PV* pulmonary veins, *PVP* pulmonary venous pressure, *PVR* pulmonary vascular resistance (mean PAP–PAWP/cardiac output), *RA* right atrium, *RV* right ventricle, *TPG* transpulmonary gradient (mean PAP–PAWP), *Wu* Wood unit. *Courtesy International Society for Heart and Lung Transplantation, reproduced with permission*

16 % had perioperative death, though among operative survivors, there was no difference in long-term survival compared to expected survival from life tables. Therefore, despite the increased operative risk, the authors conclude the long-term benefits of AVR outweigh the risks for patients with severe PH associated with AS [49]. Similarly, in patients referred for transcatheter aortic valve replacement (TAVR), PH is common, improves after correction of AS, and is associated with increased perioperative risk [50, 51].

Left Ventricular Assist Device Implantation

Irreversible pulmonary hypertension is a contraindication to heart transplant. In patients with advanced heart failure complicated by significant Cpc-PH who would otherwise be candidates for heart transplant, LVAD implantation can be used to decrease left ventricular filling pressures and thereby allow pulmonary vascular remodeling and reduction of pulmonary arterial pressures. The use of LVAD has been shown to

improve both the mean PA pressure and PVR over weeks to months regardless of the specific type of LVAD used [52–57] (Table 1). In a study of 35 patients with fixed pulmonary hypertension and $PVR > 3.5$ Wu, Zimpfer et al. found that mean PVR decreased from 5.1 to 2.0 Wu at 6 weeks and mPAP decreased from 44.0 to 18.4 mmHg, with 69 % of patients able to proceed to successful heart transplant [52]. In patients bridged with an LVAD, most authors have found that post-heart transplant survival is similar in patients with and without pre-LVAD pulmonary hypertension [55, 56], though these are small studies that may be underpowered to detect significant differences.

Pharmacologic Therapy for PH-LHD

Clear epidemiologic evidence demonstrating an association between development of PH and decreased survival in patients with LHD has led to multiple trials evaluating the

Table 1 Selected studies of ventricular assist device for PH-LHD

Author and year	Number	Design/Population	LVAD model	PVR or PVRI	mPAP	Outcome
Zimpfer, 2007	35	Fixed PH, PVR >3.5 Wu	MicroMed DuraHeart Novacor	Pre, 5.1±2.6 3 days, 2.9±1.3 6 weeks, 2.0±0.8	Pre, 44.0±6.2 3 days, 28.6±7.3 6 weeks, 18.4±4.3	Successful OHT in 24 (69 %), on VAD 210±83 days 1-year survival post-OHT 95 %
Haft, 2007	34	Indication for LVAD, 3 months follow-up	• HM I (16), mPAP ↓ 37±8 to 20±8 mmHg • HM II (18), mPAP ↓ 35±9 to 20±6 mmHg • CI ↑, PVRI ↓			Exercise capacity similar between device groups; Echo indices better with XVE
Patel, 2008	77	Retrospective comparison of post-VAD RV failure at 1,3, and 6 months	• HM I (43), no significant change in PVRI or mPAP • HM II (34), ↓mPAP ↓ at 1, 3, 6 months; PVRI ↓ at 1 month			Similar incidence of RV dysfunction between devices Fewer HM II patients required RVAD/inotrope support
Torre-Amione, 2010	9	Retrospective: TPG>15 mmHg	Pulsatile (2) Axial flow (7)	• HM I (43), no significant change in PVRI, mPAP • HM II (34), mPAP ↓ at 1, 3, 6 months; PVRI ↓ at 1 month		No difference in 1-year survival for patients with pre-VAD TPG>15 vs. TPG <15
Alba, 2010	54	Retrospective comparison of LVAD patients with vs. without fixed PH	HM XVE HM II Novacor	Fixed PH group: • sPAP ↓ from 56±8 to 31±8		No difference in post-transplant RV failure between patients with and without fixed PH
Gupta, 2014	35	Retrospective analysis of consecutive LVAD patients, RHC performed pre-LVAD, and 100.7±61.4 post-LVAD	HVAD	Pre, 3.7±2.4 Post, 2.2±1.1	Pre, 38.8±7.7 Post, 22.9±7.7	36 % developed post-VAD RV failure. RV failure associated with worse survival

CI cardiac index, HM HeartMate, HVAD HeartWare continuous-flow LVAD, mPAP mean pulmonary arterial pressure, PVR pulmonary vascular resistance, PVRI pulmonary vascular resistance index, OHT orthotopic heart transplantation, PH pulmonary hypertension, RHC right heart catheterization, RV right ventricle, TPG transpulmonary gradient

effects of drugs used primarily for PAH in PH-LHD. To date, no therapy targeting Cpc-PH has been shown to improve outcomes in this population, and in some cases there even been signals for adverse outcomes. Table 2 summarizes the key clinical trials of PH therapies for PH-LHD.

Prostacyclins

Continuously infused epoprostenol is a pulmonary and systemic vasodilator with antiplatelet effects and commonly used in the treatment of advanced PAH. Early studies in HFrEF found acute reduction in the PAWP, PVR, and systemic vascular resistance (SVR), with associated increase in cardiac output (CO). These findings lead to the Flolan International Randomized Survival Trial (FIRST), which randomized 471 patients with New York Heart Association Functional Class (NYHA) class IIIB or IV HFrEF to epoprostenol or standard care [58]. Although subjects randomized to epoprostenol experienced significant hemodynamic improvement, the trial was stopped early due to a strong trend toward decreased survival in the epoprostenol arm.

Endothelin Receptor Antagonists

Endothelin is a potent vasoconstrictor and a primary mediator of both groups 1 and 2 PH. Endothelin receptor antagonists (ERAs) induce vasorelaxation as well as antifibrotic, antiproliferative, and anti-inflammatory effects. They are commonly used in the treatment of group I PH. Initial studies of ERAs in HFrEF suggested an early hemodynamic improvement [59] and prompted larger clinical studies in patients with HF. Unfortunately, multiple clinical trials of various ERAs including bosentan, darusentan, enrasentan, sitaxsentan, and tezosentan have all failed to show improvement in clinical outcomes among patients with HFrEF [60–63]. The MELODY-1 trial (NCT8017311) is currently randomizing patients with left ventricular dysfunction and Cpc-PH to macitentan vs. placebo. This phase 2 trial is the first to specifically target patients meeting criteria for Cpc-PH. Endothelin receptor antagonists have not been well evaluated in PH-LHD due to etiologies other than HFrEF; however, there is no physiologic reason to suspect better outcomes than what was observed in HFrEF. At this time there is no clear role for ERAs in the management of PH-LHD.

Table 2 Selected randomized, controlled trials of pulmonary vasodilators in LHD

Drug/Trial	Patients	Design	1° Endpoint	Results
Epoprostenol FIRST (1997)	NYHA IIIB/IV, EF <25 % <i>n</i> =471	IV epoprostenol mPA >25 mmHg (RHC) F/u >1 year	Mortality	Terminated early due to increased mortality
Bosentan REACH-1 (2005)	NYHA III/IV, EF <35 %, 6MWT <375 m <i>n</i> =370	F/u 6 months	Change in clinical status	Terminated early due to LFTs and edema
Bosentan ENABLE (unpublished, 2002)	NYHA IIIB/IV EF <35 % <i>n</i> =1613	F/u 18 months	Mortality+HF hospitalization	No benefit Concern for increased HF hospitalization
Tezosentan VERITAS (2007)	Admitted HF Mean EF 29 % <i>n</i> =1448	IV tezosentan F/u 1 week	Mortality+worsening HF	No benefit No difference in dyspnea
Darusentan HEAT-1 (2002)	NYHA III, EF <35 %, PAWP >12 mmHg, CI <2.6 L/min/m ² <i>N</i> =179	Dose-ranging F/u 3 weeks	Change in PAWP and CI	Increased CI and decreased SVR, with no significant change in mPAP, PVR, or PAWP. Increased risk of worsening HF at higher doses
Darusentan EARTH-2 (2004)	NYHA II-IV EF <35 % <i>n</i> =642	Dose-ranging F/u 6 months	LV remodeling (MRI) Clinical events	No benefit
Macitentan MELODY-1 (NCT8017311)	LV dysfunction, Cpc-PH		Fluid retention+worsening NYHA functional class	Enrolling
Tadalafil PITCH-HF (NCT01910389)	EF <40 % sPAP >40 mmHg <i>n</i> =2102	F/u 54 months	Time to CV death or HF hosp	Suspended; did not meet enrollment milestones
Sildenafil SilHF (NCT01616381)	EF <40 % sPAP >40 mmHg <i>n</i> =210	F/u 24 weeks	Global assessment, 6MWT	Enrolling
Sildenafil RELAX (2013)	NYHA II-IV EF >50 % <i>n</i> =216	Mean sPAP=41 mmHg (no enrollment criteria related to PA pressure); F/u 26 weeks	Peak oxygen consumption	No benefit in 1° or 2° endpoints
Riociguat LEPHT (2013)	NYHA II-IV EF <40 % <i>n</i> =201	Dose-ranging mPAP >25 mmHg (RHC) F/u 16 weeks	Mean PAP	1° not met Improved MLWHF ↑CI & SV ↓PVR & SVR

6MWT six-minute walk test, CI cardiac index, CV cardiovascular, EF ejection fraction, F/u follow-up LFTs liver function tests, mPAP mean pulmonary artery pressure, NYHA New York Heart Association Functional Class, PCWP pulmonary artery wedge pressure, PVR pulmonary vascular resistance, RHC right heart catheterization, sPAP systolic pulmonary arterial pressure, SV stroke volume, SVR systemic vascular resistance. Adapted from International Society of Heart and Lung Transplantation with permission

Phosphodiesterase Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors increase cGMP and improve both hemodynamics and functional capacity in PAH [64]. The acute effects of sildenafil administration in patients with PH-HFrEF include selective pulmonary arterial vasodilation with a decrease in pulmonary arterial pressure and PVR, accompanied by an increase in cardiac index [65]. In a 12-week study of patients with HFrEF and elevated PVR, sildenafil at a dose of 25 to 75 mg TID decreased PVR and TPG while increasing CO with no effect on PAWP. This was associated with improved functional capacity at 12 weeks

[66]. This and other early studies lead to the design of the Phosphodiesterase Type 5 Inhibition With Tadalafil Changes Outcomes in Heart Failure (PITCH-HF) trial, a large multi-center study powered to evaluate the effect of PDE-5 inhibition on survival and hospitalizations in HFrEF. Unfortunately, this very important trial was terminated early due to inadequate enrollment. The Sildenafil versus Placebo in Chronic Heart Failure (SilHF) trial is currently enrolling patients with NYHA classes II–III heart failure, left ventricular ejection fraction (LVEF) <40 %, and sPAP >40 mmHg. Two hundred ten subjects will be randomized to sildenafil 40 mg TID vs. placebo [67]. The primary endpoints are patient global

assessment and six-minute walk distance rather than morbidity and mortality.

Similar benefits have been reported in patients HFpEF. In a study by Guazzi et al., 44 patients with HFpEF and PASP >40 mmHg were randomized to sildenafil 50 mg TID or placebo [68]. At 6 months, subjects randomized to sildenafil had a significant improvement in mean PA pressure, right ventricular function, right atrial pressure, pulmonary vascular resistance, pulmonary artery wedge pressure (PCWP), and cardiac index. These improvements were maintained at 12 months. The multicenter Phosphodiesterase-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure (RELAX) Trial randomized 216 subjects with heart failure and LVEF >50 % to sildenafil vs. placebo [69]. Treatment with sildenafil did not improve exercise capacity or clinical status. A key aspect of RELAX is the lack of enrollment criteria related to PA pressures. Therefore, RELAX should be considered a trial of sildenafil in HFpEF, not PH-LHD.

Despite a wealth of data demonstrating hemodynamic and clinical improvement from treatment of PH-LHD with PDE-5 inhibitors, no large-scale studies addressing this specific question have been completed. Until such a trial is performed, clinical guidelines are unlikely to recommend routine use of PDE-5 inhibitors in PH-LHD. That said, there may be particular clinical scenarios in which off-label use of PDE-5 inhibitors is reasonable in the management of PH-LHD. In an open-label study of patients undergoing heart transplant evaluation, those with persistently elevated PVR after LVAD implantation who were treated with sildenafil (titrated to an average dose of 51.9 mg TID) saw significantly greater reduction in PVR compared to those not receiving sildenafil, with an average improvement from 5.87 to 2.96 Wu [70]. Similarly, in a study of ten patients with post-LVAD PH and failure to wean from inhaled nitric oxide or inotropic support, sildenafil was

associated with a rapid decrease in sPAP and successful weaning from support [71]. Table 3 summarizes key findings from studies evaluating the effects of sildenafil in LVAD patients. Clinical applications such as this one are unlikely to be evaluated in large-scale studies, and given the current evidence many centers have successfully used PDE-5 inhibitors in the management of patients with severe PH requiring LVAD as bridge to heart transplantation [70].

Soluble Guanylate Cyclase Stimulators

Riociguat is a soluble guanylate cyclase (sGC) stimulator with vasodilatory, antifibrotic, and anti-inflammatory effects [72] that was recently shown to improve outcomes in subjects with both PAH [73] and chronic thromboembolic pulmonary hypertension [74]. The DILATE trial randomized 39 subjects with clinically stable HFpEF (EF >50 %), mean PA pressure ≥ 25 mmHg, and PCWP >15 mmHg to placebo or riociguat (0.5, 1, or 2 mg) [75]. The primary outcome was the peak decrease in mean PA pressure from baseline up to 6 h. There was no significant change in peak decrease with riociguat vs. placebo. There were improvements in several secondary endpoints including stroke volume and right ventricular end-diastolic area.

The Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial (LEPHT) randomized 201 subjects with group 2 PH and HFrEF to riociguat or placebo [76]. There was no difference in the primary endpoint of mPAP. However, both cardiac index and stroke volume index increased in the riociguat group (with no change in heart rate or blood pressure), along with decreases in both SVR and PVR as well as improvement in quality of life. Although the evidence base supporting riociguat in PH-LHD is sparse, initial findings have been encouraging.

Table 3 Studies of PDE-5 inhibitors for treatment of persistent PH after LVAD

Author and year	Number	Design/Population	Findings
Klodell, 2007	10	<ul style="list-style-type: none"> Retrospective review Post-LVAD PH Sildenafil given at the discretion of the primary team for failure to wean iNO or inotropic support 	<ul style="list-style-type: none"> sPAP decreased within 90 min of administration ($p < 0.05$) No change in SBP, MAP, SVR, or HR All 8 patients weaned from iNO within 12 h All 10 patients weaned from inotropic support within 72 h
Tedford, 2008	138	<ul style="list-style-type: none"> 58 patients with no decrease in PVR 1–2 weeks post LVAD 26 consecutive patients received sildenafil (mean dose 52 mg TID) 32 controls 	<ul style="list-style-type: none"> Sildenafil group (12–15 weeks post-LVAD): PVR decreased by 5.87 ± 1.9 to 2.96 ± 0.92 Wu* mPAP decreased by 36.5 ± 24.3 to 24.3 ± 3.6 mmHg* PVR was significantly lower in sildenafil vs. control groups Sildenafil resulted in improved RV function (dP/dT; TAPSE) vs. control

HR heart rate, iNO inhaled nitric oxide, SBP systolic blood pressure, TAPSE tricuspid annular plane systolic excursion

* $p < 0.01$

Conclusions

The last 10 years have seen increased recognition of PH-LHD as a contributor to poor outcomes and a potential target for therapy. New definitions and terminology, particularly the emphasis on the DPG, reflect an improved understanding of the underlying pathophysiology of PH-LHD. However, further evaluation of the DPG and other novel hemodynamic parameters will help refine our definitions and classification of PH-LHD. In patients with persistent PH despite optimization of left-sided pressures, therapy targeting the pulmonary vasculature is promising, though in the absence of supporting data from large-scale clinical trials this practice remains off-label and best reserved for select clinical scenarios. Hopefully, large clinical trials will help clarify the role of PH-specific therapies and identify the patients most likely to benefit from treatment with these agents.

Compliance with Ethics Guidelines

Conflict of Interest Van N. Selby declares that he has no conflict of interest.

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