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CONTEMPORARY REVIEW

Therapeutic Challenges and Emerging Treatment Targets for Pulmonary Hypertension in Left Heart Disease

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ABSTRACT: Pulmonary hypertension (PH) attributable to left heart disease (LHD) is believed to be the most common form of PH and is strongly associated with increased mortality and morbidity in this patient population. Specific therapies for PH-LHD have not yet been identified and the use of pulmonary artery hypertension-targeted therapies in PH-LHD are not recommended. Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, and prostacyclins have all been studied in PH-LHD with conflicting results. Understanding the mechanisms underlying PH-LHD could potentially provide novel therapeutic targets. Fibrosis, oxidative stress, and metabolic syndrome have been proposed as pathophysiological components of PH-LHD. Genetic associations have also been identified, offering additional mechanisms with biological plausibility. This review summarizes the evidence and challenges for treatment of PH-LHD and focuses on underlying mechanisms on the horizon that could develop into potential therapeutic targets for this disease.

Key Words: heart failure ■ mechanisms ■ pathophysiology ■ pulmonary hypertension ■ treatment

Pulmonary hypertension (PH) attributable to left heart disease (LHD) has historically been defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg and a mean pulmonary artery wedge pressure (PAWP) >15 mm Hg, determined by right heart catheterization (RHC).[1] However, the 6th World Symposium on Pulmonary Hypertension has recently recommended to reconsider the definition of PH by lowering the mPAP cutoff based on accumulating data indicating that an mPAP of 20 mm Hg is a more appropriate threshold for abnormal pulmonary artery pressure.[2] The major hemodynamic feature differentiating PH attributable to LHD from other forms of PH is the elevation in the PAWP, which estimates left atrial pressure and provides an indirect measure of left ventricular function.[1] However, caution should be used when interpreting PAWP since it only estimates left ventricular end diastolic pressure, which is considered the gold standard measurement of left ventricular filling pressure. Previous studies have shown that PAWP can incorrectly classify patients with PH potentially attributable to measurement techniques or patient characteristics such as hypoxemia, ventilation, and obesity.[3–7] PH-LHD can occur in patients with heart failure (HF) with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and left-sided valvular disease. It falls within the World Health Organization classification of Group 2 PH. Although its prevalence is not well determined, it is believed to be the most common form of PH accounting for up to 70% of PH cases.[8–11] The estimated prevalence of PH in HFpEF is collectively reported by multiple studies and registries to range between 36% to 80%, irrespective of the method for PH diagnosis.[12–16] As for patients with HFrEF, the prevalence of PH has been reported to be anywhere from 40% to 75%.[17,18] Variations in PH definitions and, most importantly, in diagnostic modalities are the main reasons for a poorly defined prevalence of PH-LHD. Nevertheless, it is important to identify PH in LHD because it is strongly associated with increased mortality and morbidity in this patient population.[8–11] Although optimizing the

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Nonstandard Abbreviations and Acronyms

CpcPH	combined pre- and postcapillary pulmonary hypertension
ERAs	endothelin receptor antagonists
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ID	inhibitor of DNA binding
IpcPH	isolated post-capillary pulmonary hypertension
LHD	left heart disease
mPAP	mean pulmonary artery pressure
PADN	pulmonary artery denervation
PAH	pulmonary arterial hypertension
PASP	pulmonary artery systolic pressure
PAWP	pulmonary artery wedge pressure
PDE5	phosphodiesterase-5
PH	pulmonary hypertension
RHC	right heart catheterization

treatment of the underlying LHD can reduce the severity of PH,[17–19] specific therapies for PH in LHD have not yet been identified. Treatments that specifically target PH in LHD could slow its progression and potentially improve disease severity, leading to far better clinical outcomes. This review focuses on the challenges of discovering optimal therapies for PH-LHD and underlying mechanisms on the horizon that could develop into potential therapeutic targets for this disease.

PATHOPHYSIOLOGY AND DIAGNOSIS

The elevation of mPAP in patients with PH-LHD is initially a manifestation of LHD; it results from an elevation in left atrial or ventricular filling pressures, which are consequences of systolic or diastolic left ventricular dysfunction.[20] PH-LHD can be divided into 2 subcategories, defined as isolated post-capillary PH (IpcPH) and combined pre- and post-capillary PH (CpcPH). In IpcPH, the mPAP is passively elevated because of increased left-sided filling pressure which congests the pulmonary circulation. In CpcPH, mPAP is elevated from increased left-sided filling pressures in addition to pulmonary vascular disease secondary to pulmonary vasculature remodeling and vasoconstriction. To further sub-classify all forms of PH, the 6th World Symposium on PH suggested including a pulmonary vascular resistance (PVR) ≥3 WU into the definition of pre-capillary PH with mPAP >20 mm Hg, regardless of underlying etiology.[2] In fact, the Symposium's task force on PH attributable to left heart disease suggested defining (1) IpcPH as a PAWP >15 mm Hg and mPAP >20 mm Hg, and PVR <3 WU and (2) CpcPH as a PAWP >15 mm Hg and mPAP >20 mm Hg, and PVR ≥3 WU.[2] Other measures that have been used to differentiate CpcPH and IpcPH include the transpulmonary gradient (=mPAP–PAWP; with values >12–15 mm Hg indicating CpcPH) and the diastolic pressure gradient (=pulmonary artery diastolic pressure–mean pulmonary arterial wedge pressure; with values >7 mm Hg indicating CpcPH).[1] Although the elevation in mPAP is attributable to increase in left heart filling pressures in the majority of patients with IpcPH, early pulmonary vascular remodeling can still occur.[21] The resulting reduction in pulmonary artery compliance leads to stiffness in the pulmonary vasculature, subsequently increasing PVR and right ventricular afterload.[22] On the other hand, the elevation in mPAP in patients with CpcPH is disproportionate to the pressure resulting from the left heart filling pressure transmission and the increase in mPAP is usually more severe than with IpcPH.[21] This subgroup of patients develops pulmonary vascular disease attributable to chronic vasoconstriction and pulmonary vasculature remodeling.[23] Chronic contraction of the right heart against the increased pulmonary artery pressure can lead to right ventricular contractile impairment and afterload mismatch, resulting in right heart dysfunction on top of left ventricular dysfunction.[24] CpcPH also exhibits features of distal pulmonary artery hypertrophic remodeling, fibrosis, and luminal occlusion, and the degree of pulmonary vascular remodeling may be associated with increased PVR and reduced pulmonary artery compliance.[25] The increase in pulmonary hemodynamic severity observed in CpcPH is often proportional to the increase in right ventricular dysfunction and has been shown to be independent of PAWP when contrasting IpcPH and CpcPH.[26] This suggests that the precapillary component in CpcPH may be a result of additional mechanisms at the arterial level.[21,26,27] The lower prevalence of right ventricular dysfunction in IpcPH is also paralleled by an overall better prognosis and survival compared with CpcPH.[28] Characteristics such as estimates of vascular compliance and right ventricular function have been associated with PH-LHD prognosis, suggesting that additional measures could be included to characterize patients with this disease.[17,29–32]

Patients with PH-LHD often present with symptoms related to their underlying LHD and right ventricular dysfunction. While non-specific, patients often complain of fatigue, progressive shortness of breath with exertion, edema of the lower extremities, as well as shortness of breath with lying flat (orthopnea) and bending over (bendopnea).[1] It is difficult to distinguish IcpPH, CpcPH and uncomplicated LHD based on physical examination alone, but patients with CpcPH may present with jugular venous distention, ascites, and peripheral

edema once they progress to right ventricular dysfunction which can be determined by echocardiographic findings of a dilated and dysfunctional right ventricle.[33] PH is often suspected in patients with LHD when echocardiography suggests right heart dilation, right ventricular dysfunction, or moderate-to-severe tricuspid regurgitation with an elevated right ventricular systolic pressure >35 mm Hg.[1] In patients with PH-HFpEF, a low diffusion capacity of the lung for carbon monoxide also suggests worse progression of the disease and increased risk for mortality.[34] The differential diagnosis of PH-LHD includes other conditions underlying PH that could also be present concomitantly with LHD. These conditions include chronic thromboembolic disease, pulmonary arterial hypertension (PAH), and other underlying lung diseases such as chronic obstructive pulmonary disease.[1] RHC remains the gold standard to differentiate PH-LHD from other forms of PH, particularly by the assessment of the PAWP.[1] To rule out chronic thromboembolic disease as a contributing factor for PH, a ventilation/perfusion scan is also recommended as HF presents with a hypercoagulable state.[1] RHC is indicated if there is evidence of right ventricular dysfunction on the echocardiography, if the cause of PH is unclear, or if advanced HF therapies are considered to support treatment decisions.[1] Once a comprehensive hemodynamic profile is obtained from the RHC, the use of PVR alone has strongly been recommended for the identification of the subtypes of PH-LHD.[2] The 2 conditions that are sometimes confused clinically are PH-LHD and PAH; but advanced age, obesity, diabetes mellitus, hypertension, and coronary disease are more likely associated with PH-LHD than PAH.[16] A pre-test likelihood score of LHD based on clinical risk factors should be included in the decision process leading to RHC.[20] A recent study showed a gradual increase in circulating microRNA-204 (miR-204), which is known to promote proliferation in pulmonary artery smooth muscle cells, across the pulmonary vasculature in patients with PAH and not in PH-LHD.[35] This offers a potential novel strategy to diagnose and better discern these 2 clinical groups of PH, although it is not clear whether the patients with PH-LHD belonged to the IpcPH or CpcPH subtype.[35] Growing evidence shows that the real difficulty is in differentiating CpcPH from PAH in the presence of LHD because of their similarities in some clinical and hemodynamic characteristics. In patients with suspected LHD and a PAWP of 13 to 15 mm Hg, provocative testing—by exercise or fluid challenge when exercise is not feasible—is recommended to identify occult LHD.[20] Similar to PAH, right ventricular dysfunction and pulmonary artery remodeling develops more frequently in CpcPH compared with IpcPH.[28] Some evidence also suggests that patients with CpcPH could share similar age, body mass index, natriuretic peptide levels, 6-minute walk distance, and comorbidities with idiopathic PAH.[36] These findings, along with the histopathology of CpcPH, resulted in the hypothesis that PH could be a continuum ranging from PAH to PH-LHD with CpcPH in the middle.[36] Whether this is true, and whether real distinctions between the different subtypes of PH cannot be made remain to be confirmed.

TREATMENTS

Although PAH and PH-LHD have some similarities in presentation, confusing them in the clinical setting can lead to inappropriate therapeutic care of patients with PH.[33] The 6th World Symposium on Pulmonary Hypertension strongly recommends against the use of PH-targeted therapies for PH-LHD because based on the available evidence PH-targeted therapies have failed to show benefit in these patients.[2] There are currently no treatments for PH-LHD, and the standing paradigm for its treatment consists of optimizing the management of the underlying disease[37] such as aggressively treating HF and performing valvular repair when indicated to reduce the progression of the disease.[1,38] The first line agents recommended for HFrEF consist of beta-blockers in combination with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors as well as sodium-glucose cotransporter-2 inhibitors for their mortality benefit.[39–41] As for patients with HFpEF, the current guidelines recommend optimizing treatment of comorbidities and use of diuretics for congestion since randomized controlled trials have not resulted in beneficial therapies in this setting yet.[39,40] Metabolic syndrome and other risk factors for cardiovascular comorbidities should be managed as well.[1,38] Finally, other disorders such as chronic obstructive pulmonary disease, pulmonary embolisms, and sleep apnea could also lead to PH and should be adequately treated.[1,38]

Multiple PAH-targeted medications across different drug classes have been studied in PH-LHD. The following sections review the results of trials investigating the various drug classes for the treatment of PH-LHD (Table 1).

Endothelin Receptor Antagonists

Activation of endothelin receptors on endothelial and vascular smooth muscle cells leads to potent vasoconstriction.[64] Increased expression of endothelin-1 in vascular endothelial cells has been associated with PH development, rendering it a potential treatment target in this disease.[65] In fact, endothelin receptor antagonists (ERAs) such as bosentan, ambrisentan, and macitentan have been approved for the treatment of PAH. Some evidence has also suggested an association of

Table 1. Completed and Ongoing Randomized Controlled Trials in PH-LHD

Endothelin Receptor Antagonists				
Study	**Drug**	**Population**	**Primary Outcome**	**Result**
REACH-1[42]	Bosentan titrated to 500 mg twice daily for 26 wk	NYHA class IIIB-IV for at least 2 mo, LVEF within 6 mo <35%, hospitalization for HF within 12 mos or inability to walk >375 m during a 6-min walk test n=370	Change in clinical status after 26 wk of therapy (death, hospitalization for HF, NYHA status change)	Terminated early because of liver toxicity
ENABLE[43]	Bosentan 125 mg twice daily	NYHA class IIIB-IV for at least 2 mo, LVEF <35%, hospitalization for HF within 12 mo or inability to walk >375 m during a 6-min walk test n=1613	Clinical status at 9 mo (assessed by the hierarchical clinical composite; death from any cause or hospitalization for HF)	No improvement, early and increased fluid retention
Kaluski et al[44]	Bosentan slowly titrated to 125 mg twice daily	NYHA class IIIb–IV, LVEF <35%, SPAP ≥40 mm Hg, supine SBP ≥100, hospitalization for HF within 6 mo before randomization n=94	Change from baseline to wk 20 in SPAP	No significant improvement
MELODY-1[45]	Macitentan 10 mg once daily for 12 wk	CpcPH within 12 wk before or during screening, LVEF ≥30%, NYHA class II or III, a 6-min walk distance (6MWD) ≥150 m and an optimized stable dose of oral diuretic(s) n=63	Significant fluid retention or worsening in NYHA functional class from baseline to end of treatment	Numerically more frequent fluid retention with macitentan
HEAT[46]	Darusentan 30, 100, and 300 mg once daily for 3 wk	LVEF ≤35%, Clinical signs of HF, NYHA class III, PAWP ≥12 mm Hg, CI ≤2.6 $L{\cdot}min^{-1}{\cdot}m^{-2}$ n=157	Change from baseline of CI and PAWP 3 wk after start of therapy	Improvement in CI after 3 wk of treatment
EARTH[47]	Darusentan at 10, 25, 50, 100, or 300 mg daily for 24 wk	NYHA class II–IV, LVEF <35% n=642	Change in LVESV at 24 wk from baseline	No significant improvement
Phosphodiesterase type 5 inhibitors				
Behling et al[48]	Sildenafil 50 mg 3 times daily for 4 wk	LVEF ≤40% n=19	Cardiopulmonary exercise test parameters (chronic effect), echocardiographic-derived SPAP, and plethysmography-derived forearm blood flow	Decrease in SPAP at 4 wk
Guazzi et al[49]	Sildenafil 50 mg 3 times daily	LVEF ≥50%, sinus rhythm, and no hospitalization in the 6 mo preceding recruitment, SPAP ≥40 mm Hg n=44	Pulmonary hemodynamics and RV performance	Significant improvements in mPAP and RV function
Guazzi et al[50]	Sildenafil 50 mg 3 times daily	HF with mild-to-moderate PH (mPAP within 25–35 mm Hg) and EOB n=32	EOB changes, hemodynamic measurements	Improvement in EOB, mPAP, PAWP, PVR

(*Continued*)

Table 1. Continued

Endothelin Receptor Antagonists				
Study	**Drug**	**Population**	**Primary Outcome**	**Result**
RELAX[51]	Sildenafil 20 mg 3 times daily for 12 wk, followed by 60 mg, 3 times daily for 12 wk	HF with NYHA class II–IV, NT-proBNP ≥400 pg/mL or elevation in LV filling pressures at the time of an NT-proBNP <400 pg/mL n=216	Change in peak oxygen consumption after 24 wk of therapy	No improvement
Lewis et al[52]	Sildenafil 25 mg 3 times daily uptitrated every 2 wk to 75 mg 3 times for a total of 12 wk	LVEF <40%, NYHA class II to IV, secondary PH as defined by a mPAP >25 mm Hg n=34	$\dot{V}O_2$	Improvement of $\dot{V}O_2$ at peak exercise and of change in peak $\dot{V}O_2$ with increase in CO
Hoendermis et al[53]	Sildenafil, titrated to 60 mg 3 times daily for 12 wk	PH (mPAP >25 mm Hg and PAWP >15 mm Hg) due to HFpEF (LVEF ≥45%) n=52	Change in mPAP	No improvement
SIOVAC[54]	Sildenafil 40 mg 3 times daily for 6 mo	PH (mPAP ≥30 mm Hg), successful surgical or percutaneous valvular replacement or repair procedure, a stable HF clinical condition n=200	Composite clinical score combining death, HF hospitalization, change in functional class, and patient global self-assessment	Worsening in clinical outcomes
Soluble guanylate cyclase stimulators				
SOCRATES-REDUCED[55]	Vericiguat 1.25, 2.5, 5, and 10 mg once daily for 12 wk	LVEF <45% within 4 wk of a worsening chronic HF event n=456	Change from baseline to week 12 in log (NT-proBNP)	No improvement
SOCRATES-PRESERVED[56]	Vericiguat 1.25 or 2.5 mg fixed doses, or 5 or 10 mg titrated from a 2.5 mg starting dose, once daily for 12 wk	LVEF≥45% within 4 wk of a worsening chronic HF event n=477	Change from baseline to week 12 in log (NT-proBNP) and LAV	No improvement
VICTORIA[57]	Vericiguat 10 mg once daily	NYHA class II, III, or IV, LVEF <45%, elevated natriuretic peptide level n=5050	Composite of death from cardiovascular causes or first hospitalization for heart failure.	Reduction in primary outcome event
LEPHT[58]	Riociguat 0.5, 1, or 2 mg 3 times daily for 16 wk	LVEF ≤40%, mPAP ≥25 mm Hg n=201	Placebo-corrected change from baseline at week 16 in mPAP	No improvement
DILATE-1[59]	Riociguat 0.5, 1, or 2 mg in single oral doses	HF with LVEF >50%, mPAP ≥25 mm Hg PAWP >15 mm Hg n=39	Peak decrease in mPAP from baseline up to 6 h	No improvement
Prostacyclin analogs				
FIRST[60]	Epoprostenol infusion of 2 ng/kg per min for 15 min with incremental doses of 2 ng/kg per min until dose-limiting adverse experiences	NYHA class IIIB-IV, LVEF <25% n=471	Survival	Terminated early because of significant decreased survival
Ongoing clinical trials				
NCT03624010[61]	Levosimendan 2.5 mg/mL diluted to achieve a 50 µg/min solution for infusion	HFpEF n=36	Long-term (2 y) clinical safety measured by number of adverse events	Pending

(*Continued*)

Table 1. Continued

Endothelin Receptor Antagonists				
Study	**Drug**	**Population**	**Primary Outcome**	**Result**
NCT03015402[62]	Sodium Nitrite 40 mg by mouth TID 3 times daily for 10 wk	PH-HFpEF n=26	mPAP during submaximal exercise	Pending
SPHERE-HF[63]	Mirabegron 50 mg by mouth once daily for 16 wk	HF, CpcPH, NYHA class II–IV n=80	Change in PVR	Pending

6MWD indicates 6-minute walking distance; CI, cardiac index; CO, cardiac output; CpcPH, Combined post- and pre-capillary pulmonary hypertension; DILATE-1, Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure; EARTH, EndothelinA Receptor Antagonist Trial in Heart Failure; ENABLE, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; EOB, exercise oscillatory breathing; FIRST, Flolan International Randomized Survival Trial; HEAT, Heart Failure Endothelin A Receptor Blockade Trial; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LAV, left atrial volume; LEPHT, Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial; LHD, left heart disease; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MELODY-1, Macitentan in subjects with combined prE- and post-capiLlary pulmOnary hypertension due to left ventricular DYsfunction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; REACH-1, Research on Endothelin Antagonism in Chronic Heart Failure Study; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; RV, right ventricular; SBP, systolic blood pressure; SIOVAC, Sildenafil for Improving Outcomes after VAlvular Correction; SOCRATES-PRESERVED, SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF; SOCRATES-REDUCED, SOluble guanylate Cyclase stimulatoR in heArT failurE patientS With REDUCED EF; SPAP, systolic pulmonary artery pressure; SPHERE-HF, β3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction; and $\dot{V}O_2$, peak oxygen uptake.

endothelin-1 with HF development and progression, further emphasizing the importance of investigating its role in the treatment of PH-LHD.[66–68] The ERAs bosentan, macitentan, and darusetan have not shown significant benefit in clinical trials of PH-LHD and have raised concern for greater adverse effects.[42–47] The goal of the REACH-1 (Research on Endothelin Antagonism in Chronic Heart Failure) pilot study was to investigate the long-term clinical outcomes of bosentan in patients with advanced HFrEF, but it was terminated before reaching the recruitment goal because of high rates of liver function abnormalities in the treatment arm.[42] Although the study did report significant improvement in the New York Heart Association class with bosentan in the subgroup of patients who were followed up for the entire study period, it also showed a higher risk of death and HF worsening with bosentan early after treatment initiation.[42] In the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial, endothelin antagonism with bosentan in patients with advanced HFrEF did not improve the New York Heart Association functional class or the global clinical assessment of patients at 9 months, but resulted in early and increased fluid retention manifested as increased peripheral edema and weight gain leading to a significant increase in hospitalization for HF.[43] Bosentan also failed to show significant improvement in systolic pulmonary arterial pressure (PAP) or tricuspid regurgitation velocity in patients with PH-LHD in a multicenter randomized controlled trial, while showing a higher rate of serious adverse events.[44]

Macitentan, another ERA, was investigated in the MELODY-1 (Macitentanin Subjects with Combined Pre- and Post-Capillary Pulmonary Hypertension Due toLeft Ventricular Dysfunction) randomized controlled trial for patients with left HF with CpcPH.[45] After 12 weeks of treatment, macitentan did not significantly improve PVR, PAWP, or mean right atrial pressure compared with placebo.[45] Although not statistically significant, macitentan also resulted in numerically more adverse events such as significant fluid retention and worsening New York Heart Association functional class.[45] Finally, while darusentan improved cardiac index in patients with HF after 3 weeks of treatment in the HEAT (Heart Failure Endothelin A Receptor Blockade Trial), it did not significantly reduce PAWP, mPAP, PVR, or right atrial pressure. Similar to other ERAs, it also was associated with significantly higher rates of adverse events in the higher dosage groups.[46] Unlike the HEAT trial, the EARTH (Endothelin Receptor Antagonist Trial in Heart Failure) trial did not show any improvement of cardiac remodeling or clinical status of patients with chronic HF treated with darusentan for 24 weeks in addition to first line HF therapies.[47] Only 1 of the above trials included patients with PH suspected by echocardiography and none showed

a long-term improvement in clinically significant outcomes from ERAs in PH-LHD. Overall, most trials of ERAs in PH-LHD showed a higher rate of adverse events, with some being terminated early because of safety concerns. This has led to the conclusion that ERAs lack efficacy and safety rendering them inappropriate for the treatment of PH-LHD.

Phosphodiesterase-5 Inhibitors

Inhibiting phosphodiesterase-5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate, results in vasodilation.[1] The pulmonary vasculature has significant levels of PDE5; therefore, the potential benefit of this class of drugs has been investigated in PH-LHD.[69,70] PDE5 inhibitors have been widely investigated for the treatment of PH in LHD. Sildenafil showed promising results in the earlier smaller trials. In patients with HFrEF, treatment with sildenafil resulted in significantly lower pulmonary artery systolic pressure (PASP) estimated by echocardiography in 1 study.[48] In another small study, patients with HFpEF with right ventricular failure treated with sildenafil had a significant improvement in their mPAP and right ventricular function and a reduced right atrial pressure and PAWP.[49] Chronic treatment with sildenafil significantly decreased mPAP, PAWP, and PVR compared with placebo in patients with HF with exercise oscillatory breathing.[50] In the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial, 216 patients with HFpEF were randomized to sildenafil or placebo.[51] At 24 weeks, sildenafil showed no improvement compared with placebo in the primary outcome of exercise capacity or in the secondary outcomes including change in 6-minute walk distance, left ventricular mass, diastolic dysfunction, and a composite of death, cardiac/renal hospitalization, or increased HF symptoms. Although not statistically significant, there was a small increase in vascular adverse events such as headache, flushing, and hypotension in the sildenafil group.

In a study of patients with PH-LHD, sildenafil significantly improved PVR, cardiac output, 6-minute walk distance, and exercise capacity.[52] In another study investigating patients with HFpEF with PH, sildenafil did not improve mPAP, PAWP, cardiac output, and peak oxygen consumption compared with placebo.[53] In the SOVIAC (Sildenafilfor Improving Outcomes after VAlvular Correction) study, sildenafil was investigated in patients with PH-LHD who had undergone a successful mitral and/or aortic valve replacement or repair and had evidence of persistent precapillary PH after valvular surgery.[54] Treatment with sildenafil resulted in significantly worse clinical outcomes including death and HF hospitalization compared with placebo.[54]

Multiple meta-analyses have combined the results of studies evaluating the effects of various PDE5 inhibitors or sildenafil alone in PH-LHD.[71–75] The results were consistent across the meta-analyses with PDE5 inhibitors resulting in significant improvements in mPAP, PVR, LVEF, exercise capacity, and quality of life in patients with HFrEF, but not in patients with HFpEF.[71–75] However, most studies that included patients with HFpEF had a relatively small sample size of this subset; therefore, more research is required to determine if PDE5 inhibitors benefit this group.[71–75]

The studies showing benefit with PDE5 inhibitors included patients with HFrEF or HFpEF with right ventricular failure or both HFpEF and HFrEF. Patients with HFpEF without right ventricular failure did not appear to benefit despite the larger sample size. Right ventricular dysfunction is a predictor of poor prognosis in HFrEF and HFpEF, but is more marked in HFrEF than HFpEF for a given level of PH.[76] Therefore, the findings on PDE5 inhibitors attest to the hypothesis that the presence of right ventricular dysfunction might predict a beneficial response to PDE5 inhibitors.[77]

Soluble Guanylate Cyclase Stimulators

While PDE5 inhibitors exert vasodilation by slowing cyclic guanosine monophosphate degradation, soluble guanylate cyclase stimulators enhance its production resulting in increased vasodilation.[78] Vericiguat was given at multiple doses and compared with placebo in the SOCRATES-REDUCED (Soluble Guanylate Cyclase Stimulator in Heart Failure Patients With REDUCED EF) and the SOCRATES-PRESERVED (Soluble Guanylate Cyclase Stimulator in Heart Failure Patients with PRESERVED EF) trials which included patients with HFrEF and patients with HFpEF, respectively.[55,56] The goal of these trials was to determine the optimal dose and tolerability of vericiguat in worsening chronic HF. In the SOCRATES-REDUCED trial, vericiguat was well tolerated, but it did not result in significant changes in NT-proBNP (N-terminal pro-b-type natriuretic peptide) compared with placebo, nor in echocardiographic parameters and in clinical outcomes such as all cause death or the composite of cardiac death or HF hospitalizations.[55] In the SOCRATES-PRESERVED trial, vericiguat did not reduce NT-proBNP levels and did not improve left atrial volume compared with placebo, but it was well tolerated and was associated with improvements in the patients' quality of life according to the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score used in the study.[56] The stepwise addition of vasodilatory drugs to the regimen of patients with HF raises their risk of adverse events because of pronounced lowering of blood pressure specifically in patients with worsening HF and a lower baseline blood pressure.[79–81] The VICTORIA (Vericiguat Global

Study in Subjects with Heart Failure with Reduced EjectionFraction) trial was a multicenter study that randomized 5050 patients with HFrEF and evidence of worsening symptoms to vericiguat or placebo.[57] The composite of death from cardiovascular causes or HF hospitalizations was significantly lower in the vericiguat group compared with the placebo group.[57] There were no statistically significant differences in serious and non-serious adverse events between the 2 treatment arms.[57] PH is a manifestation of advanced HF, so the beneficial effects of vericiguat on the progression of HF could also prove valuable if it results in significant reduction of disease advancement and potential prevention of PH development.

Riociguat, another soluble guanylate cyclase stimulator, was given at multiple doses to patients with PH-HFrEF in the LEPHT (Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial).[58] Although it did not result in significant improvements in mPAP at any dose, it was well tolerated and it significantly improved cardiac index, stroke volume index, and pulmonary and systemic vascular resistance in the highest dose group.[58] The effect of riociguat in patients with PH-HFpEF were evaluated in the DILATE-1 (Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure) trial and were comparable with its effect in PH-HFrEF.[59] Riociguat was well tolerated and improved stroke volume and systolic blood pressure, but it did not have significant effects on mPAP and PVR.[59] Given the tolerability of vericiguat and some encouraging clinical benefits in the setting of LHD, future trials could prove valuable in investigating additional end points in PH-LHD such as mortality and hospitalizations to evaluate the progression of the disease. However, the lack of efficacy of riociguat on mPAP could also indicate that soluble guanylate cyclase stimulators do not improve PH in LHD, possibly because of the advanced stage of the disease. In contrast the beneficial effects of soluble guanylate cyclase stimulators in HFrEF could be through the improvement of cardiac index, stroke volume, and total pulmonary resistance.

Prostacyclin Analogs

Prostacyclin is primarily produced by endothelial cells; it stimulates vasodilation and has antithrombotic and antiproliferative effects, which can improve outcomes in HF.[82] Epoprostenol, a synthetic analog of prostacyclin, was approved for the treatment of PAH, and its potential to reduce pulmonary vascular resistance coupled with its beneficial effect on right ventricular dysfunction in PAH provided a basis to investigate it in PH-LHD. FIRST (Flolan International Randomized Survival Trial) investigated the use of intravenous epoprostenol in patients with severe HFrEF for the improvement of hemodynamic and clinical outcomes.[60] Although epoprostenol resulted in a significant increase in cardiac index, decrease in PAWP, and decrease in systemic vascular resistance, the study was stopped early because of a strong trend toward decreased survival with epoprostenol.[60] The majority of death events were caused by progressive congestive heart failure, with the hypothesis that vasodilators could result in short-term benefit but activate deleterious neurohormonal systems and lead to renin secretion in the longer term.[60] Treprostinil, a newer prostacyclin analog is approved for the treatment of PAH and improves pulmonary hemodynamics in PAH.[83]

In animal models, prostacyclin analogs and prostacyclin precursors appear to reverse metabolic syndrome and prevent HFpEF development, respectively.[84,85] This raised the possibility that treprostinil could have beneficial effects on the pulmonary vasculature and on systemic metabolic features in PH-LHD. Although it has not been studied in human subjects with PH-LHD yet, it has shown some promising results in animal studies. Treprostinil was studied in mouse and rat models of PH-HFpEF with features of metabolic syndrome and diabetes mellitus, which are commonly seen in patients with PH-LHD.[86] In the mouse model, 16-week treatment with treprostinil significantly improved hyperglycemia and trended to lower pulmonary pressures.[86] Early treatment (concurrently with semaxinib [SU5416] exposure) of the rat model with treprostinil significantly improved hyperglycemia and pulmonary pressures.[86] Late treatment (7 weeks after a single injection of SU5416) of the rat model with treprostinil and metformin lowered hyperglycemia and improved cardiac function through the activation of AMP-activated protein kinase in skeletal muscle and the right ventricle, but did not reduce pulmonary pressures.[86] Whether the beneficial effect of treprostinil will be translated in human patients remains to be seen, but the data suggests that treatments targeting skeletal muscle liver kinase B1/sirtuin-3-AMP-activated protein kinase and right ventricle AMP-activated protein kinase could potentially be developed for the prevention of metabolic syndrome-associated PH-LHD.[86] In contrast, the FIRST trial in which continuous infusion of epoprostenol failed to show any benefit, included patients with HFrEF who had not necessarily developed PH yet. This could mean that prostacyclin analogs could work better in PH-HFpEF, which typically demonstrates different comorbidities and subsequent development such as in the setting of metabolic syndrome and diabetes mellitus compared with HFrEF which normally presents as a consequence of myocardial infarction and ischemia.

A recent study evaluated the pooled effect of multiple PAH-targeted therapies, mostly PDE5 inhibitors

and ERAs, on the disease progression of patients with CpcPH.[87] The majority of the included patients had HFpEF and did not experience improvement in symptoms, echocardiographic parameters, or functional capacity. However, they did experience higher morbidity and mortality with PAH-targeted medications.[87] A meta-analysis pooling the results of multiple PH-targeted therapies such as PDE5 inhibitors, prostanoids, ERAs, and soluble guanylate cyclase stimulators has concluded that PDE5 inhibitors may improve exercise capacity in patients with LHD, but that all drug classes resulted in a higher risk for adverse events.[88]

Pulmonary Artery Denervation

Pulmonary Artery Denervation (PADN) is a catheter-based technique aimed at ablating the densely innervated regions in or near the pulmonary artery that are involved in the baroreceptor reflex resulting in PH.[89,90] Following successful animal studies showing preclinical efficacy of PADN, it was tested in patients with PAH who were resistant to medical therapies and was shown to be safe and efficacious in improving their hemodynamic parameters and functional capacity.[89,90] Recently, studies in preclinical models of PH-LHD have shown that the upregulation of alpha-1 and downregulation of beta adrenergic receptors in the lung tissue of PH-LHD-induced rats was counteracted by PADN.[91] In a phase II trial of mixed PH etiologies including PH-LHD, PADN resulted in overall improvements in mPAP and 6-minute walking distance.[92] Finally, a multi-center trial of PADN efficacy on CpcPH led to a decrease in mPAP, systolic PAP, and diastolic PAP, and to an increase in cardiac output and 6-minute walking distance.[93] PADN also resulted in a reduction of clinical worsening and hospitalizations compared with the control group.[93] However, PADN was compared with sildenafil, which is not approved for the treatment of PH-LHD; therefore, the results are disputable. Overall, PADN shows promise in different PH types including PH-LHD, but further research is required to assess its long-term safety and clinical outcomes.[93]

Ongoing Clinical Trials

Levosimendan is a calcium sensitizer that enhances myocardial contractility and results in arterial, venous, and coronary vasodilation.[94] Its positive inotropic effect does not increase myocardial oxygen demand and its vasodilatory effect results in the protection of the myocardium from ischemia and a reduction in right ventricular preload and afterload.[94] These 3 pharmacological effects together could target the pathophysiology of PH-LHD. Levosimendan is currently being studied in a phase II trial of patients with PH-HFpEF who will receive a weekly dose and be periodically evaluated over 2 years for primary outcomes of adverse events and secondary outcomes of effectiveness such as 6-minute walk test, New York Heart Association functional class, and incidence of death and hospitalizations.[61] The early results of the HELP (Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF) trial show that levosimendan reduced resting mPAP, and resting and exercise central venous pressure and pulmonary capillary wedge pressure (PCWP); it also increased the 6-minute walking distance, demonstrating a promising role in the treatment of PH-LHD.[95] However, further studies are necessary to evaluate the long-term effects of levosimendan in this setting.[95]

Another phase II clinical trial is currently investigating the efficacy of oral sodium nitrite compared with placebo in patients with PH-HFpEF. Exogenous nitrite has vasodilatory effects and has shown to reduce pulmonary pressures.[96,97] The primary outcome of interest in the phase II clinical trial is mPAP during submaximal exercise after 10 weeks of treatment.[62] In fact, inhaled sodium nitrite has shown to improve pulmonary, right atrial, and pulmonary capillary wedge pressures in patients with PH-HFpEF in a pilot phase II study. This effect was mainly achieved by lowering left and right ventricular filling pressures and increasing pulmonary artery compliance. This adds to the notion of the physiological benefit of exogenous administration of nitrite in PH-LHD.[98]

Stimulation of the β3 adrenergic receptor has proven to be cardioprotective in multiple animal models of HF by attenuating hypertrophic remodeling through nitric oxide synthase and possibly through reduced sodium-potassium pump stimulation in the heart.[99–101] The SPHERE-PH (β3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure) trial is currently investigating the effects of mirabegron, a clinically available β3 adrenergic agonist approved for the treatment of overreactive bladder, on pulmonary hemodynamics, clinical, biochemical and cardiac imaging measures in CpcPH secondary to HF.[63] The investigators of the SPHERE-PH trial had previously found that β3 adrenergic agonists significantly reduced PVR and improved right ventricular function in a porcine model of IpcPH.[102] These studies propose new approaches to treat PH in LHD and could potentially overcome the limitations and failures of the previous studies.

Finally, the National Institutes of Health/National Heart, Lung, and Blood Institute launched the PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) initiative with the goal of increasing our understanding of different PH classifications based on biological characteristics.[103] The study will enroll 1500 participants

with PH, with or without heart and lung diseases, and healthy volunteers.[103] The broad hypothesis of the study is that the combination of epidemiological and clinical features with -omic data will update the classification of pulmonary vascular diseases.[103] In addition to the main hypothesis, the different participating centers will be focusing on specific hypotheses.[103] At the end of the study, it is expected that the data collected will serve as a valuable source to investigators seeking to identify therapeutic targets.[103]

THERAPEUTIC CHALLENGES

Despite a better understanding of the subtypes of PH-LHD, many challenges still exist slowing the discovery of effective therapies. As discussed above, the heterogeneity in the presentation and the different phenotypes observed within PH-LHD could contribute to the failure of treatment studies. Furthermore, the contribution of the underlying cardiac disease along with the multiple comorbidities that many patients with PH-LHD present with, could complicate studies of PH progression and act as complex confounders when assessing clinical outcomes. Finally, an important element needed for the discovery of new therapies is the availability of animal models that correlate to the clinical presentation of PH-LHD. While monocrotaline-induced PH results in right ventricular dysfunction and HF in a rat model, it manifests changes not associated with human HF.[104,105] Similarly, pulmonary aortic banding leads to pulmonary hypertension and right ventricular hypertrophy with greater tricuspid regurgitation,[106] but left-sided disease characteristics are generally not achieved.[106] A SU5416/obese ZSF1 rat model of PH-HFpEF has recently been developed by combining endothelial injury with metabolic syndrome features.[107] The SU5416-induced pulmonary endothelial injury resulted in elevated pulmonary pressure that overall improves the model. Although this model more closely resembles the clinical phenotype of human PH-HFpEF, it is expensive and limited in the number of molecular procedures that can be performed on it.[107] Therefore, the development of a high-fat diet–induced pulmonary hypertension in AKR/J mice proved to be significant.[108] This mouse model parallels the clinical presentation of patients with PH-HFpEF with key clinical features such as aging, metabolic syndrome, elevated right ventricular systolic pressure, and left ventricular end-diastolic pressure.[108] It was also validated and shown to be reliable and reproducible, offering new possibilities for the mechanistic study of this disorder and the testing of potential new therapies.[108] The recent development of more accurate preclinical models of PH-LHD should accelerate not only our understanding of the disease, but also the development of specific and efficacious therapies.

POTENTIAL NOVEL TREATMENT TARGETS

The proper diagnosis of PH-LHD may be challenging, yet it has direct therapeutic consequences. Since our understanding of IpcPH and CpcPH is still growing, the studies mentioned above could have missed distinguishing these subtypes. This could potentially have masked significant effects of a drug on one of the subtypes. Also, CpcPH and PAH have similar right ventricular dysfunction and pulmonary artery remodeling,[28] which could explain some of the conflicting results observed if patients with CpcPH benefit from some of the PAH-targeted therapies and patients with IpcPH do not. Moreover, even with the current recommendations of optimizing the treatment of the underlying disease, clinically significant PH in LHD still remains.[109] The failure of previous clinical trials in demonstrating safety or efficacy of PAH therapies in the setting of PH-LHD further highlights the need for additional work to be conducted. Finding potential treatment targets specific for PH-LHD requires a better understanding of the underlying mechanisms associated with PH-LHD.

Compared with PAH, the underlying pathophysiology and histopathological associations with PH-LHD are limited and not yet understood. Small exploratory studies have added to our understanding of underlying mechanisms in PH-LHD (Figure 1, Table 2). In 108 patients with PH-LHD, global pulmonary vascular remodeling with severe medial and intimal thickening of the veins similar to patients with pulmonary veno-occlusive disease was identified.[110] The severity of PH, based on PASP from echocardiography and transpulmonary gradient and PVR from RHC, was strongly correlated with the degree of pulmonary venous remodeling.[110] Extensive venous remodeling in pulmonary veno-occlusive disease can increase the transcapillary hydrostatic pressure gradient and lead to alveolar edema precipitated by increases in pulmonary arterial blood flow attributable to PAH-targeted vasodilators.[111] These findings could explain the predisposition of patients with HF to worsening pulmonary edema in response to pulmonary vasodilators that is similar to pulmonary veno-occlusive disease. The findings also provide the pathobiology of pulmonary venous remodeling as a potential treatment target for PH-LHD.[110] A mouse model of aortic constriction-induced left HF and advanced PH exhibited increased wet and

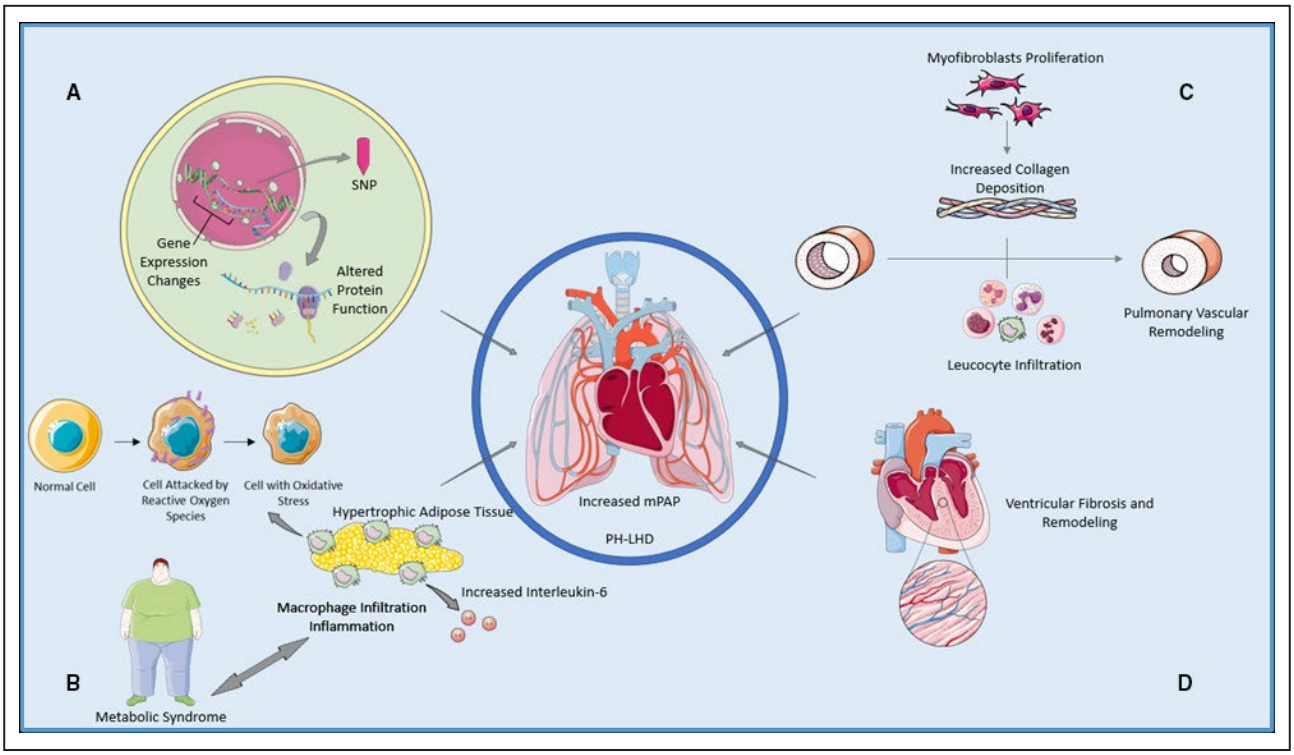

Figure 1. Underlying mechanisms and potential treatment targets for pulmonary hypertension in left heart disease.
A, Gene expression changes or genetic polymorphisms, resulting in altered protein function, have been associated with pulmonary hypertension (PH) in left heart disease (LHD) prompting a new approach in understanding the possible mechanisms of its development by studying the function of the affected proteins. **B**, Metabolic syndrome has been suggested as a predisposing factor for PH in LHD. It can result in macrophage accumulation and increased interleukin-6 levels, implicating inflammation as a potential treatment target. Oxidative stress has been proposed to contribute to the development of right ventricular remodeling and PH in LHD with reactive oxygen species potentially serving as disease progression biomarkers and/or therapeutic targets. **C**, The degree of pulmonary vascular remodeling, attributable to fibrosis and myofibroblast proliferation and leukocyte infiltration, has been correlated with the severity of PH development in LHD quantified by increased pulmonary hemodynamics. **D**, Right ventricular fibrosis in pulmonary hypertension in heart failure with preserved ejection fraction has been associated with worsening right ventricular diastolic volume and right ventricular free wall strain and has offered a distinct mechanism and treatment target compared with other forms of PH. mPAP indicates mean pulmonary artery pressure; PH-HFpEF, pulmonary hypertension in heart failure with preserved ejection fraction; PH-LHD, pulmonary hypertension in left heart disease; and SNP, single nucleotide polymorphism.

dry lung weights that were not associated with pulmonary edema, but with pulmonary fibrosis and remodeling.[25] The extensive increase in the proportion of muscularized lung vessels was seen with myofibroblast proliferation and leukocyte infiltration.[25] In addition to pulmonary fibrosis, right ventricular fibrosis in PH-HFpEF has been associated with worsening right ventricular diastolic volume and right ventricular free wall strain.[112] This indicates an inadequate structural and functional remodeling of the right ventricle.[112] However, right ventricular fibrosis was not associated with total pulmonary resistance as it was in PAH.[112] This suggests that the diffuse right ventricular fibrosis in PH-HFpEF may be out of proportion to the right ventricular afterload seen in this disease. This observation offers a distinct pathophysiology for PH-HFpEF compared with PAH.[112]

Oxidative stress has also been associated with cardiovascular diseases and, in some experimental models, reactive oxygen species have been associated with PH and right ventricular remodeling.[121–123] Increased levels of reactive oxygen species leads to higher calcium influx resulting in smooth muscle contraction and subsequent increase in PASP.[124] In addition, decreasing oxidative stress has been shown to lower PASP and improve right ventricular dysfunction in animal models.[125,126] Ghasemzadeh et al investigated the relationship between oxidative stress and PH in humans.[113] Cysteine is one of the major aminothiol compounds available in the plasma that reacts with oxidants to form cystine, which can be quantified and used as a measure of oxidative stress.[127,128] In 347 patients with HFrEF and HFpEF who underwent echocardiography, increased plasma cystine levels were associated with increased PASP even in a subgroup

Table 2. Studies Uncovering Potential Therapeutic Targets in PH-LHD

Study	Method	Results	Potential Therapeutic Target
Fayyaz et al[110]	Comparison of lung specimens of PH-HF vs controls vs patients with PVOD	Severity of PH correlated with venous and small intermediate vessel intimal thickening	Pulmonary vascular remodeling
Ghasemzadeh et al[113]	Evaluation of the relationship between PASP and plasma aminothiol oxidative stress markers	Increased plasma cystine levels associated with increased PASP	Oxidative stress
Robbins et al[114]	Comparison of the prevalence of MS features in patients with PH-LHD vs PAH	PH-LHD had a higher frequency of hypertension, obesity, diabetes mellitus, and hyperlipidemia	Metabolic syndrome
Ranchoux et al[115]	Comparison of Sham vs DD/MS rats	Precapillary PH developed in DD/MS rats only, and interleukin-6 reduction decreased pulmonary vascular remodeling and improved PH-LHD	Metabolic syndrome Inflammation
Meoli et al[116]	Comparison of transpulmonary ratio of endothelin-1 and hemodynamics in CpcPH vs IpcPH vs patients with LHD without PH	Higher transpulmonary ratio of endothelin-1 in CpcPH correlated with higher pulmonary vascular resistance	Pulmonary endothelin-1 and endothelin receptor in CpcPH
Duarte et al[117]	Comparison of hemodynamic measurements between genotype groups of rs1799983 (*NOS3*) and rs3730017 (*NOS2*) polymorphisms in patients with PH-HF	The T/T genotype at rs1799983 was associated with 10 mm Hg increase in TPG. In a combined analysis of 2 PH-HF cohorts, rs1799983 was associated with mPAP, DPG, and CpcPH status	Endothelial nitric oxide synthase
Olson et al[118]	Comparison of SPAP between genotype groups of the repeat length polymorphism in the promoter region of the *5-HTT* gene and between patients with HFand controls	A significant interaction between the HF and control groups for SPAP by genotype existed, with a significant genotype effect in patients with HF, but not in controls. The homozygous genotype for the long variant was associated with higher SPAP	Repeat length polymorphism in the *5-HTT* gene
Arwood et al[119]	Transcriptome-wide analysis comparing gene expression of PBMCs of patients with CpcPH vs IpcPH vs HF without PH	*ID1* and *ID2* genes were upregulated in the PBMCs of patients with CpcPH compared with HF without PH Cell cycle and oxidative phosphorylation pathways were significantly upregulated in CpcPH compared with HF without PH	*ID* gene family and associated pathways
Assad et al[27]	Single nucleotide polymorphisms compared between patients with PAH vs CpcPH compared with IpcPH	Seventy-five genetic variants, involved in cell structure, extracellular matrix, and immune function pathways, were shared between CpcPH and PAH	Vascular remodeling
Kelly et al[120]	Genome-wide association study to identify candidate genes associated with PH-LHD in a mouse model	Epidermal growth factor receptor gene was the most likely gene to be associated with right ventricular systolic pressure changes	Epidermal growth factor receptor gene

5-HTT indicates gene encoding for the serotonin transporter; CpcPH, combined post- and pre-capillary pulmonary hypertension; DD, diastolic dysfunction; DPG, diastolic pulmonary gradient; HF, heart failure; ID1, gene encoding the inhibitor of DNA binding 1; ID2, gene encoding the inhibitor of DNA binding 2; IpcPH, isolated post-capillary; mPAP, mean pulmonary artery pressure; MS, metabolic syndrome; NOS2, gene encoding inducible nitric oxide synthase; *NOS3*, gene encoding endothelial nitric oxide synthase; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PBMCs, peripheral blood mononuclear cells; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension attributable to left heart disease; PVOD, pulmonary veno-occlusive disease; and TPG, transpulmonary gradient.

analysis of patients with HFpEF.[113] Future studies investigating the role of plasma cystine in the prediction of PH or as a monitoring tool for the progression of the disease are needed. Also, the use of cysteine levels to follow-up PH treatment or the benefit of targeting cysteine levels to treat oxidative stress and potentially PH warrants further research.

In a small cohort of patients with PH, PH-LHD was strongly associated with metabolic syndrome compared with PAH, suggesting that metabolic syndrome is a predisposing factor for PH in patients with LHD.[114] To better understand the underlying mechanism, a new rat model of LHD was developed in which metabolic syndrome was shown to exacerbate PH measured by both echocardiography and RHC.[115] PH was also associated with macrophage accumulation, increased interleukin-6 and activation of the signal transducer and activator of transcription 3 in the lungs of the rat model and of patients with PH-LHD.[115] Reduction of interleukin-6 levels, by treatment with antibodies or metformin, reduced inflammation and pulmonary artery smooth muscle cell proliferation in vitro and in vivo and reversed pulmonary vascular remodeling in the rat model, implicating inflammation as a plausible mechanism behind metabolic syndrome-induced PH-LHD.[115]

Circulating biomarkers also have the potential to reveal underlying pathophysiology, improve phenotypic classification, or possibly identify potential treatments. One study has shown that pulmonary artery wedge blood levels of endothelin-1 were elevated in patients with HFpEF-CpcPH compared with patients with IpcPH or HFpEF without PH.[116] In addition, levels of endothelin-1 in wedge blood strongly correlated with PVR and were not exclusively defined by left ventricular filling pressures.[116] This study reiterates the notion that CpcPH could have a distinct pathophysiology from IcpPH and that endothelin receptor blockage may provide benefit in this population.[116]

Genetic approaches can prompt or can complement physiological analyses in understanding the pathobiology of complex human diseases.[129,130] Specific genetic

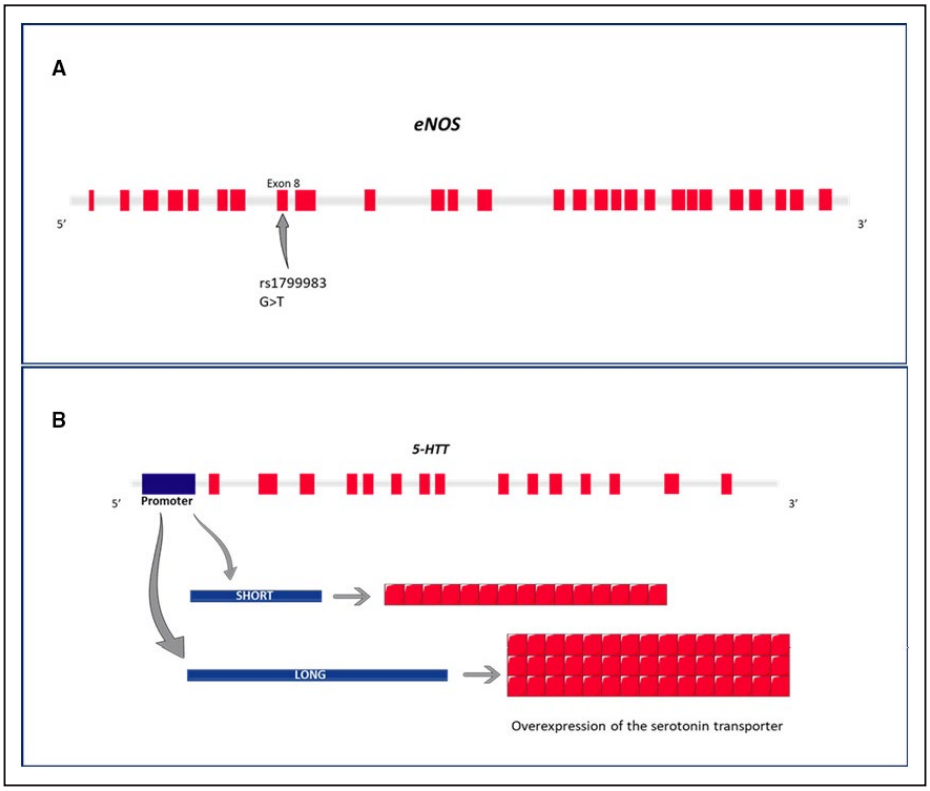

Figure 2. Potential genetic polymorphisms associated with pulmonary hypertension in left heart disease.
Red boxes represent exons and blue boxes represent the promoter region. **A**, Single nucleotide polymorphism within the gene encoding for the endothelial nitric oxide synthase enzyme has been shown to be associated with lower nitric oxide levels in humans and worse pulmonary hemodynamics in patients with pulmonary hypertension in left heart disease. **B**, Repeat length polymorphism in the promoter region of the serotonin receptor gene was associated with overexpression of the serotonin transporter and elevated pulmonary artery pressure in patients with heart failure. *5-HTT* indicates serotonin receptor gene; *eNOS*, endothelial nitric oxide synthase gene; and PH-LHD, pulmonary hypertension in left heart disease.

associations with PH-LHD have not been established yet,[1] but different hypotheses are being studied. A single nucleotide polymorphism within the gene encoding for the endothelial nitric oxide synthase enzyme has been shown to be associated with transpulmonary gradient in 2 independent cohorts of patients with PH-LHD (Figure 2A).[117] The genetic variation was also associated with diastolic pressure gradient, PVR, and mPAP in a combined analysis of both cohorts.[117] This association was not present in a separate cohort of patients with PAH nor in patients with PH attributable to lung disease, suggesting a specific linkage with PH-LHD.[117,131] This finding does have a biological plausibility since this specific polymorphism has been associated with lower nitric oxide levels in humans and endothelium-derived nitric oxide plays a major role in vascular tone regulation.[132] Clinically, this mutation has also been associated with dilated cardiomyopathy and with poorer survival in patients with HFrEF.[133,134] The possibility that low nitric oxide levels could contribute to the development of PH in LHD could explain the failure of nitric oxide stimulating drugs, suggesting that the problem could lie in the ability to produce nitric oxide leading to the hypothesis that supplying exogenous nitric oxide may be more beneficial than stimulating its synthesis.

Another biologically plausible association was demonstrated between the repeat length polymorphism in the promoter region of the serotonin transporter gene and elevated PAP in patients with HF (Figure 2B).[118] This polymorphism was associated with overexpression of the serotonin transporter and consequent serotonin uptake by pulmonary smooth muscle cells leading to an imbalance between vasoconstriction and vasodilation and contributing to the proliferation of pulmonary artery smooth muscle cells. This polymorphism was also significantly more prevalent in patients with idiopathic PAH compared with control participants.[135] This mechanism could also explain the susceptibility of patients with HF to develop PH. The evidence for serotonin and serotonin receptors in cardiovascular diseases is that they can affect the cardiovascular system in a compensatory or in a detrimental way, through vasodilation or vasoconstriction and through inotropic or arrhythmic effects.[136,137] Consequently, the cardiovascular response to serotonin agonists or antagonists has been conflicting and research into serotonin and its receptors in cardiovascular diseases is still ongoing and has generated multiple hypotheses that still need answering.

In a transcriptome-wide analysis, we recently found that the inhibitors of DNA binding (*ID*)1 and 2 genes were upregulated in the peripheral blood mononuclear cells of patients with CpcPH compared with patients with HF without PH.[119] The *ID* gene family has been previously associated with PAH and all 4 members of the ID protein family (ID1–4) are functional inhibitors of the basic helix–loop–helix transcription factors which confers them the ability to regulate cell fate determination, differentiation, and proliferation in multiple tissues including the vasculature.[138–142] In a gene set enrichment analysis, the cell cycle and oxidative phosphorylation pathways were significantly upregulated in patients with CpcPH compared with patients without PH.[119] *ID* expression is regulated by bone morphogenetic proteins, and mutations in bone morphogenetic protein receptors type II occur in a majority of patients with familial PAH.[143,144] In pulmonary artery smooth muscle cells of mouse models and patients with PAH carrying these mutations, gene expression changes of *ID* genes have been demonstrated.[145] Therefore, the involvement of these genes and associated pathways in the development of PH-LHD warrants further research to determine their potential use as therapeutic targets.

In another study comparing patients with IpcPH or CpcPH to patients with PAH, CpcPH and IpcPH had similar clinical presentations of left ventricular dysfunction.[27] In contrast, 141 genes were differentially expressed among patients with PAH and CpcPH when compared with IpcPH.[27] Increased expression of these genes in the lungs along with biologic processes relevant to vascular remodeling similar to PAH pathophysiology were observed in CpcPH.[27] Patients with CpcPH may have a genetic predisposition to pulmonary vascular disease in LHD and may be a distinct PH phenotype.

While no genome-wide association study has been reported yet in humans with PH-LHD, one was conducted in a high-fat diet-–induced mouse model of PH-LHD.[120] The goal of the study was to identify genes associated with increased right ventricular systolic pressure indicating a susceptibility to develop PH-LHD.[120] Following a network-based scoring analysis on the significantly associated genetic variants, the epidermal growth factor receptor gene as the most likely to be associated with right ventricular systolic pressure changes.[120] These findings also correlated with increased expression of the gene in the lungs of the mouse model of PH-LHD.[120] Therefore, studying the epidermal growth factor receptor gene could enhance our understanding of the underlying mechanisms behind PH-LHD and the gene could potentially serve as a therapeutic target for this disease.

FUTURE DIRECTIONS

PH in LHD is the most common form of PH and brings a poor prognosis by increasing the morbidity and mortality risk of this patient population. Despite apparent similarities with PAH, the current guidelines do not recommend PAH-targeted drugs for PH-LHD.

This is because of the failure of previous clinical trials in proving their safety and/or efficacy in the setting of PH-LHD. It is imperative to further improve our understanding of the pathophysiology and underlying mechanisms of PH-LHD to develop specific therapies for this disease and by doing so, establish an evidence-based approach for the management of patients with HF developing PH. To understand these mechanisms, it is necessary to identify biological pathways or genetic factors associated with PH-LHD. After establishing newer approaches, clinical trials focusing on outcomes such as mortality, hospitalizations, and quality of life would be necessary to correlate physiological recovery with clinical improvement.

ARTICLE INFORMATION

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