Pulmonary Hypertension in Left Heart Disease and Chronic Right Ventricular Failure

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KEYWORDS

• Pulmonary hypertension • Left heart disease • Postcapillary pulmonary hypertension • Chronic right ventricular failure • Therapeutic challenges

KEY POINTS

- Pulmonary hypertension due to left heart disease (PH-LHD) is classified as postcapillary PH, with 2 subtypes: isolated postcapillary PH and combined postcapillary and precapillary PH based on pulmonary vascular resistance.
- Right ventricular failure in PH results from chronic pressure overload, leading to maladaptive dilation, tricuspid regurgitation, and decreased cardiac output, worsening systemic congestion and heart failure.
- Diagnosis of PH-LHD relies on right heart catheterization, with pulmonary artery wedge pressure greater than 15 mm Hg indicating postcapillary PH, while exercise or fluid challenge testing can help differentiate it from pulmonary arterial hypertension.
- PH-specific therapies (PDE5 inhibitors, ERAs, and prostacyclins) have shown no clinical benefit in PH-LHD and in certain randomized studies revealed worsened outcomes due to fluid retention and hemodynamic instability.
- Emerging interventions such as interatrial shunt devices, pulmonary artery denervation, and MitraClip for severe mitral regurgitation may offer therapeutic potential but require further research for precise patient selection.

DEFINITIONS

Pulmonary hypertension (PH) is characterized by a mean pulmonary artery pressure (mPAP) greater than 20 mm Hg, as measured by right heart catheterization (RHC), according to the 6th World Symposium on Pulmonary Hypertension (WSPH).[1] PH is classified into 2 categories based on pulmonary capillary wedge pressure (PCWP) measurements: precapillary PH, which occurs when PCWP is 15 mm Hg or lower, and postcapillary PH, defined as having a PCWP greater than 15 mm Hg.[1,2] The World

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Abbreviations	
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitors
CO	cardiac output
CpcPH	combined postcapillary and precapillary pulmonary hypertension
DPG	diastolic pressure gradient
EF	ejection fraction
ERAs	endothelin receptor antagonists
GDMT	guideline-directed medical therapy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
IASD	interatrial shunt device
IpcPH	isolated postcapillary pulmonary hypertension
LA	left atrium/left atrial
LV	left ventricle
LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
mPAP	mean pulmonary artery pressure
MRA	mineralocorticoid receptor antagonist
PAC	pulmonary arterial compliance
PADN	pulmonary artery denervation
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PCWP	pulmonary capillary wedge pressure
PDE5i	phosphodiesterase type 5 inhibitors
PH-LHD	pulmonary hypertension due to left heart disease
PVD	pulmonary vascular disease
PVR	pulmonary vascular resistance
RA	right atrial
RHC	right heart catheterization
RHF	right heart failure
RV	right ventricular
RVD	right ventricular dysfunction
sGCs	soluble guanylate cyclase stimulators
SGLT2	sodium-glucose cotransporter-2
SLAS	stiff left atrial syndrome
TPG	transpulmonary gradient
TR	tricuspid regurgitation
WHO	World Health Organization

Health Organization (WHO) groups PH into 5 categories, with PH due to left heart disease (PH-LHD) classified as WHO Group 2.[2] PH-LHD typically results from conditions such as left ventricular dysfunction, valvular heart disease, or congenital and acquired left heart inflow or outflow obstruction, with left ventricular dysfunction being the most common cause, regardless of its origin.[3] From a hemodynamic perspective, postcapillary PH is further divided into 2 subtypes: isolated postcapillary PH (IpcPH) and combined post- and precapillary PH (CpcPH). IpcPH is defined by a pulmonary vascular resistance (PVR) of 3 Wood units (WU) or less, while CpcPH is characterized by a PVR greater than 3 WU.[4] The 2022 ESC/ERS guidelines removed the diastolic pressure gradient (DPG) from the definition of PH-LHD due to conflicting evidence regarding its prognostic value.[5] The 6th WSPH redefined PH by lowering the mPAP threshold to greater than 20 mm Hg and incorporating PVR into the general definition.[1]

This new classification has been adopted by the ESC/ERS guidelines but has not yet been widely integrated into international clinical trials or other guideline frameworks.

PATHOGENESIS

Pulmonary Hypertension Due to Left Heart Disease

PH-LHD is primarily caused by elevated left atrial (LA) pressure, which leads to pulmonary vascular remodeling.[6,7] The LA acts as a crucial intermediary between the left ventricle (LV) and the pulmonary circulation, facilitating LV filling and protecting the pulmonary vasculature from excessive pressure fluctuations. However, LA remodeling—characterized by increased volume, impaired contractility, and interstitial fibrosis—results in reduced compliance and a diminished ability to buffer pulmonary pressures.[8] As LA pressure increases, there is passive transmission of this pressure to the pulmonary circulation, leading to IpcPH.[8–11] In some instances, exercise-induced pulmonary hypertension worsens because of the progression of functional mitral regurgitation, further exacerbating pulmonary congestion.[12]

Chronic pulmonary venous hypertension can result in endothelial dysfunction and capillary stress failure, leading to increased vascular permeability and interstitial edema.[13] Impaired nitric oxide-dependent vasodilation in heart failure (HF) contributes to the progression of pulmonary hypertension by promoting pulmonary vasoconstriction.[14] Pulmonary vascular remodeling occurs over time, regardless of ejection fraction (EF), with autopsy studies revealing structural changes in both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).[6,8,9,15,16] However, in HFrEF, evidence from patients undergoing left ventricular assist device (LVAD) implantation suggests that PVR decreases, indicating the potential reversibility of vascular changes with optimized hemodynamics.[17] Notably, this reversibility under LVAD support may be enhanced by endothelin receptor antagonists (ERAs). The SOPRANO trial demonstrated that macitentan, an ERA, further reduces PVR in HFrEF patients with pulmonary hypertension post-LVAD implantation, with a placebo-corrected reduction of 26.1% after 12 weeks ($P = .0158$), supporting the reversibility of some vascular changes with targeted therapy.[17]

In advanced PH-LHD, persistent LA hypertension can trigger pulmonary arterial intimal thickening and medial hypertrophy, leading to increased right ventricular (RV) afterload.[18] Initially, RV hypertrophy serves as an adaptive response, but prolonged pressure overload results in maladaptive RV dilation, functional tricuspid regurgitation (TR), and right atrial (RA) hypertension, ultimately progressing to RV failure.[19,20] Compared to IpcPH, patients with CpcPH exhibit more severe RV dysfunction, higher PVR, ventilation-perfusion mismatch, and worse functional status, along with a higher risk of mortality.[21]

Pulmonary Hypertension and Chronic Right Ventricular Failure

Right heart failure (RHF) and right ventricular dysfunction (RVD) are related yet distinct conditions. RVD can exist without evident RHF, and not all cases of RVD lead to RHF. The diagnosis of RHF requires evidence of elevated RA and venous pressures, such as jugular venous distension, along with at least one of the following: compromised RV function, PH, or peripheral edema accompanied by congestive hepatomegaly.[22]

The RV is structurally and functionally different from the LV. It is a thin walled, highly compliant chamber designed to handle volume overload rather than pressure overload. The RV functions as a high-volume, low-pressure pump, generating only 25% of the LV's stroke work while propelling the same stroke volume.[23,24] RV contraction

primarily occurs longitudinally, unlike the radial contraction seen in the LV, which makes traditional imaging techniques less effective for assessing RV function.[25] The RV's ability to adapt to increased afterload is largely dependent on RV–pulmonary artery (PA) coupling, which ensures efficient energy transfer from the RV to the pulmonary circulation. However, when PVR rises due to pulmonary vascular remodeling, endothelial dysfunction, or hypoxia-related vasoconstriction, RV afterload increases, eventually leading to RV dysfunction and failure.[26,27]

Progression of Right Heart Failure in Pulmonary Hypertension due to Left Heart Disease

Chronic RHF stemming from LHD typically arises from a gradual elevation in RV afterload due to postcapillary PH. This condition is marked by an mPAP of 25 mm Hg or higher, alongside elevated left heart filling pressures, such as a PCWP of 15 mm Hg or more, or an LV end-diastolic pressure (LVEDP) of 18 mm Hg or more.[28,29] In majority of patients with HF, PH remains postcapillary and is associated with low PVR. However, certain patients may develop CpcPH resulting from vascular remodeling, endothelial dysfunction, and progressive vasoconstriction, leading to increased PVR.[15,30] The initial adaptive response to increased afterload is RV hypertrophy, which helps maintain stroke volume and reduce wall stress. As PH progresses, however, RV dilation occurs, often coupled with TR resulting from annular dilation.[31,32] As RV function declines, worsening TR leads to venous congestion, further compromising cardiac output (CO) and resulting in systemic fluid overload. In severe instances, RV dilation can cause a shift of the interventricular septum toward the LV, which elevates left heart filling pressures, impairs LV diastolic filling, and diminishes CO, ultimately exacerbating left-sided HF.[33–35]

Elevated pulmonary venous pressure and RV dysfunction are primary factors in RHF associated with PH, yet other processes also play significant roles. Neurohormonal activation can lead to fluid retention and RA volume overload, further increasing venous pressures and systemic congestion.[36] Atrial fibrillation (AF), frequently observed in patients with LHD, exacerbates RV dysfunction and PA uncoupling by altering LA filling dynamics, resulting in reduced CO due to irregular cardiac cycles.[37] Moreover, pulmonary vascular remodeling and stiffening progressively elevate RV afterload, leading to heightened RV wall stress and maladaptive structural responses.[38] Chronic RV failure can result in diminished LV filling, particularly during physical exertion, which reduces LV stroke volume and systemic perfusion, further intensifying hemodynamic instability and exercise intolerance[39] (**Fig. 1**).

Impact of PH and RHF on the Left Ventricle and Coronary Circulation

RHF in PH significantly affects LV function and coronary perfusion through several mechanisms. Diastolic ventricular interdependence, stemming from shared myocardial fibers and pericardial constraint, causes RV dilation that compresses the LV, raising LV filling pressures even when preload is reduced.[40,41] Chronic low CO and decreased LV workload contribute to LV atrophy and deconditioning, leading to reductions in LV end-diastolic volume (by ~10%–20%) and LV mass (by 5%–15%), along with decreased LV stroke volume and EF.[42–44] Furthermore, dilation of the PA in PH can compress the left main coronary artery (left main compression syndrome), resulting in myocardial ischemia and arrhythmias.[45] Notably, a PA diameter of 48 mm or greater has been associated with a 7.5 fold increased risk of sudden death in severe PH and chronic thromboembolic PH.[45]

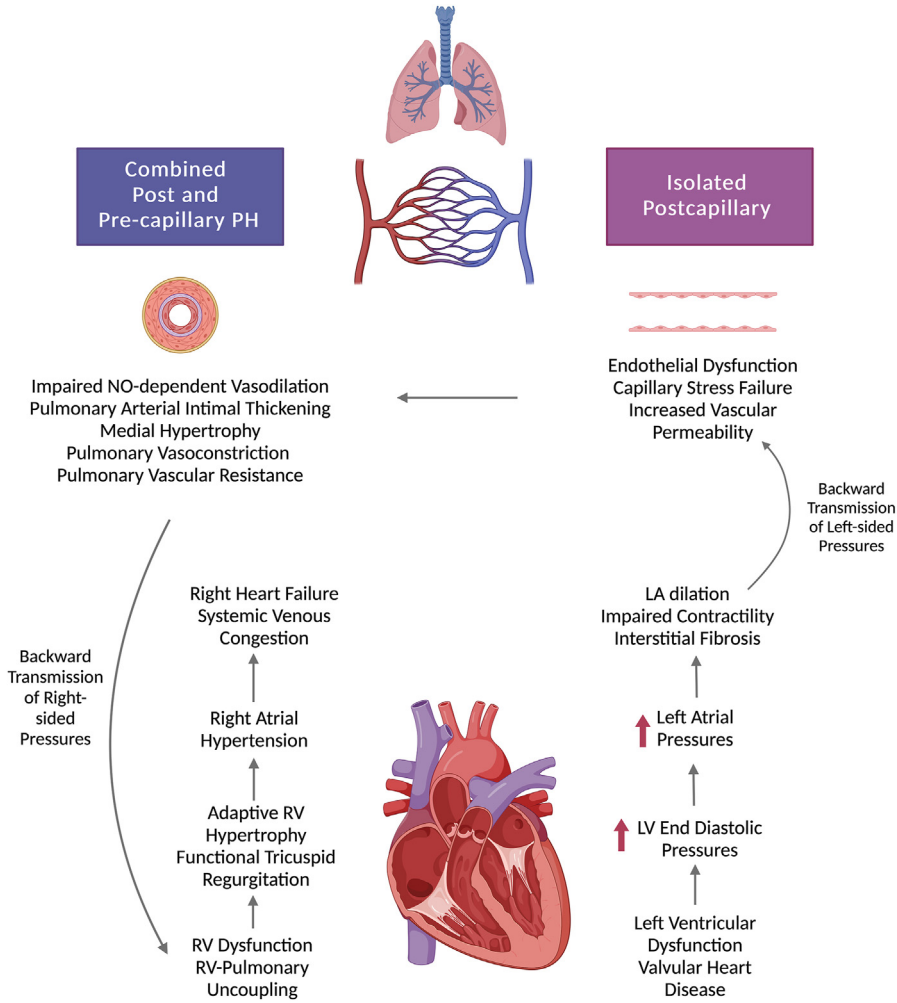

Fig. 1. Pathophysiology of pulmonary hypertension due to left heart disease.

DISCUSSION

Assessment of Pulmonary Hypertension

Accurate measurement of pulmonary artery wedge pressure (PAWP) is crucial for distinguishing between precapillary and postcapillary PH. RHC must be performed with precision, ensuring the patient is positioned supine with legs flat. The pressure transducer should be aligned with mid-chest, approximating the level of the LA,[6] and properly zeroed with the stopcock open to the patient and closed to air to eliminate extraneous pressure influences. Sedation should be avoided, as it may induce sleep-disordered breathing and alter hemodynamic measurements. Breath-holding maneuvers are discouraged due to the risk of Valsalva-induced preload changes; instead, pressures should be recorded during calm, spontaneous breathing at end-expiration to better approximate true intracardiac pressures.[46] Complete PA occlusion with a balloon-tipped catheter is essential for accurate PAWP measurement, though hybrid PA-PAWP tracings remain common despite fluoroscopic and waveform

confirmation.[21,46,47] If PAWP is elevated (>15 mm Hg), checking PAWP saturation can confirm complete occlusion.[48] While end-expiratory PAWP is generally recommended, in cases of significant respiratory variation (eg, obesity or parenchymal lung disease), averaging PAWP across the respiratory cycle may more accurately reflect LV preload.[49] Reporting both end-expiratory and respiratory cycle-averaged PAWP is advisable when respiratory variation exceeds 7 to 10 mm Hg.[49] Overall, accurate hemodynamic assessment through RHC has significant clinical implications. However, acquisition and interpretation techniques vary widely depending on operator subspecialty and experience. These differences, as observed between HF specialists and interventional cardiologists, as well as early and late career clinicians, underscore the need for standardized RHC practices. Uniform techniques are critical for reliably distinguishing PH subtypes and enhancing patient management.[50]

PAWP serves as a surrogate for left-sided filling pressures and hemodynamic congestion, though it is not always interchangeable with LVEDP.[51–53] The moderate correlation between PAWP and LVEDP can be influenced by conditions such as AF.[54] Historically, LVEDP was considered the gold standard for assessing LHD in the evaluation of PH, but PAWP more accurately reflects chronic hemodynamic congestion by capturing adaptations in LA remodeling and compliance over time.[55]

The LA's response to pressure overload varies between HFpEF, which exhibits greater LA stiffness, and HFrEF, which leads to eccentric LA remodeling.[56] LA strain, a reproducible measure of LA function, is divided into three phases: reservoir (during LV systole), conduit (early LV diastole), and booster (LA contraction at LV end-diastole).[57,58] A notable example of LA dysfunction contributing to PH is the stiff left atrial syndrome (SLAS), a rare condition often linked to extensive catheter ablation for AF.[59] SLAS is characterized by PH due to reduced LA compliance and contractility, typically manifesting years after ablation due to scarring. This syndrome presents with elevated PAWP (often with large V waves) and high mean PA pressure, yet normal LVEDP, normal mitral valve function, and no pulmonary vein stenosis—distinguishing it from other postcapillary PH causes like HFpEF or mitral stenosis. In SLAS, the interplay of LA stiffness and downstream pulmonary vascular changes further complicates hemodynamic interpretation, emphasizing the need for comprehensive invasive and non-invasive assessments to guide management, which may include diuretics or, in refractory cases, innovative interventions like atrial septostomy.[59] Overall, understanding changes in LA structure and function is critical for assessing PH risk, differentiating PH subtypes in HF, and identifying therapeutic targets.

While the DPG and transpulmonary gradient (TPG) were historically used to classify PH in LHD, they have been omitted from recent consensus guidelines. Nevertheless, elevated TPG and PVR remain key prognostic markers in advanced HF and may influence cardiac transplantation eligibility.[60] A systemic vasodilator challenge is recommended for patients with PA systolic pressure 50 mm Hg or greater, TPG 15 mm Hg or greater, or PVR 3 WU or greater, provided systolic blood pressure exceeds 85 mm Hg, to assess PH severity and response to afterload reduction.[61]

While PVR accounts for CO in the assessment of pulmonary vascular disease (PVD), hemodynamic loading, congestion, and pulmonary vessel recruitment can also influence TPG and DPG, albeit to a lesser degree.[62] No single hemodynamic variable can completely capture PVD in PH-LHD, and these complexities are often overlooked in preclinical models of PH-LHD.[63]

Hemodynamic Phenotypes of Pulmonary Hypertension in Left Heart Disease

PH-LHD is traditionally viewed as a progressive continuum, beginning with IpcPH and evolving into CpcPH as pulmonary vascular remodeling and vasoconstrictive

responses develop. However, this model lacks longitudinal hemodynamic data, and emerging evidence suggests an alternative phenotype-based classification influenced by pulmonary arterial hypertension (PAH) risk factors.[64,65] Some patients with mildly elevated PAWP but disproportionately high PVR and DPG may possess an underlying PAH phenotype, coupled with coexisting cardiometabolic risk factors, which complicates strict classification as PH-LHD. These individuals exhibit pathophysiologic and genetic overlaps with those fitting into PAH criteria, despite technically meeting the criteria of PH-LHD due to elevated PAWP.[54,66]

CpcPH appears to represent an intermediate phenotype between postcapillary pulmonary hypertension and PAH, sharing characteristics of pulmonary vascular remodeling and endothelial dysfunction but lacking the plexiform lesions characteristic of PAH.[66] Genetic studies support a "two-hit hypothesis," suggesting that hemodynamic stress alone is insufficient for pulmonary vascular remodeling; a secondary genetic, metabolic, or hormonal factor is required to drive pulmonary arteriopathy.[66]

In clinical practice, LHD and PAH are rarely mutually exclusive, as patients often present with multiple cardiometabolic risk factors such as obesity, sleep apnea, AF, hypertension, tobacco use, and diabetes.[67] These comorbidities are prevalent even in younger populations (<50 years), blurring the distinction between PH-LHD and PAH.[68,69] Additionally, connective tissue diseases—known risk factors for both LHD and PAH—further complicate phenotypic classification. Strict hemodynamic definitions often fail to account for overlapping disease mechanisms, potentially excluding patients from PAH-directed therapies who might otherwise benefit.

Diagnostic Considerations

Due to the similarities between PH-LHD and PAH phenotypes, provocative testing can help with classification, especially when precapillary pulmonary hypertension criteria are met but left heart disease is suspected. Exercise RHC is being used more frequently, with a pulmonary arterial wedge pressure (PAWP) over 25 mm Hg during supine ergometry or over 20 mm Hg during upright testing suggesting left heart disease.[70] Additionally, a multipoint PAWP-CO slope greater than 2 mm Hg/L/min indicates the presence of concealed left heart disease.[71] However, these criteria often overlap, which limits their diagnostic accuracy.

The 6th WSPH recommends fluid challenge testing to differentiate between Group 1 (PAH) and Group 2 (PH-LHD) pulmonary hypertension. An abnormal PAWP greater than 18 mm Hg following the administration of 500 to 1000 mL of normal saline over 5 to 10 minutes (or 7 mL per kg based on body weight) is suggestive of PH-LHD.[48] Given the complexities involved in distinguishing between PH-LHD phenotypes, further research is necessary to improve diagnostic algorithms and to identify patients who may benefit from PAH-specific therapies, even if they meet PH-LHD criteria (**Fig. 2**).

Management and Therapeutic Challenges in PH-LHD

Although PAH and PH-LHD present with overlapping clinical characteristics, accurately distinguishing between them is essential for effective treatment decisions. Misdiagnosing PH-LHD as PAH can result in the inappropriate administration of PAH-specific therapies, which multiple clinical trials have shown to provide no therapeutic benefit in patients with PH-LHD and, in some instances, lead to increased adverse effects. The WSPH strongly advises against the use of these PH-targeted therapies in PH-LHD, citing consistent evidence of inefficacy and potential harm in this patient group.[72] Beyond the clinical implications, the misuse of these therapies also places a substantial financial strain on health care systems and patients. PAH-specific

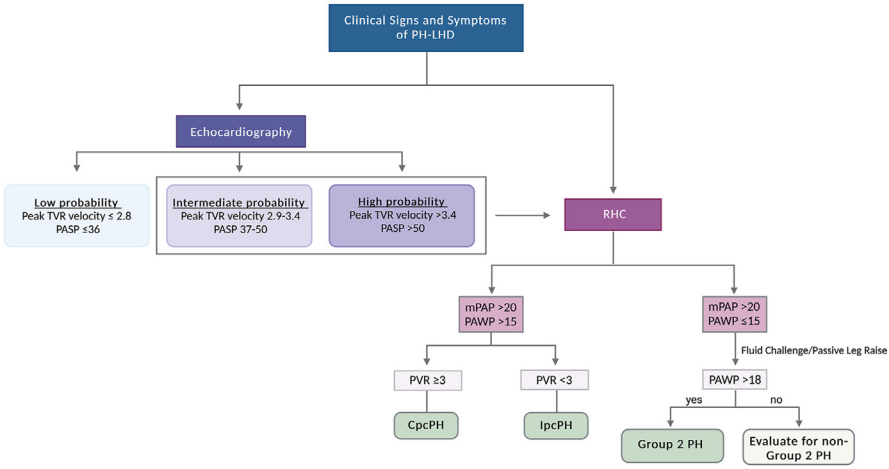

Fig. 2. Diagnosis of pulmonary hypertension due to left heart disease. CpcPH, combined postcapillary and precapillary pulmonary hypertension; DPG, diastolic pressure gradient (mm Hg); IpcPH, isolated postcapillary pulmonary hypertension; mPAP, mean pulmonary artery pressure (mm Hg); PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure (mm Hg); PH-LHD, pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance (WU); RHC, right heart catheterization; TVR, tricuspid valve regurgitation.

treatments are often high-cost interventions, and their unwarranted use in PH-LHD escalates expenses without improving outcomes. Therefore, precise differentiation between PAH and PH-LHD is critical not only to ensure clinically appropriate care but also to mitigate the significant and avoidable economic burden associated with these therapies.

Currently, no approved pharmacologic treatments exist for PH-LHD. The mainstay of management involves optimizing the underlying LHD through aggressive HF treatment and valvular intervention when necessary to slow disease progression.[4,73,74] For patients with HFrEF, guideline-directed medical therapy (GDMT) may include beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors, all of which have demonstrated improvements in survival and reductions in hospitalizations.[73–75] In contrast, management in HFpEF primarily focuses on controlling comorbidities, optimizing volume status with diuretics, and implementing lifestyle modifications, as no pharmacologic therapies aside from SGLTi have shown definitive benefits in randomized clinical trials.[73–75]

It is also crucial to address several other factors that worsen the progression of PH-LHD and HF. Metabolic syndrome and cardiovascular risk factors, such as hypertension, diabetes, and obesity, play a significant role by increasing cardiac workload and vascular stress. Obstructive sleep apnea aggravates both conditions through intermittent hypoxia, heightened sympathetic activity, and added strain on the heart. AF further contributes by disrupting cardiac rhythm, reducing pump efficiency, and promoting hemodynamic instability. Additionally, chronic inflammation, volume overload from renal dysfunction, and untreated comorbidities like chronic obstructive pulmonary disease can accelerate disease worsening. Addressing these interconnected factors is critical to mitigate progression and improve outcomes in PH-LHD and HF.[4,73–75]

Clinical Trials of PH-Targeted Therapies in PH-LHD

ERAs such as bosentan, ambrisentan, and macitentan are approved for PAH but have failed to show benefits in PH-LHD and raised safety concerns in clinical trials. Studies, including REACH-1, ENABLE, MELODY-1, and HEAT, did not demonstrate an improvement in hemodynamics but did show an increase in adverse events, particularly fluid retention and worsening HF, which led to the early termination of some trials.[76–81]

Phosphodiesterase type 5 inhibitors (PDE5i) initially showed promise in small studies. Sildenafil demonstrated reductions in pulmonary artery systolic pressure, improved RV function, and decreased PVR in patients with HFrEF and HFpEF with RV failure.[82–89] However, larger trials, such as RELAX, did not demonstrate clinical improvement in patients with HFpEF, while Sildenafil for Improving Outcomes after Valvular Correction trial (SIOVAC) resulted in worsening HF for patients with persistent PH-LHD after valvular surgery.[85,88] These findings suggest that RV dysfunction may be a predictor of response to PDE5i, with benefits potentially limited to specific PH-LHD phenotypes.

Soluble guanylate cyclase stimulators (sGCs) such as riociguat and vericiguat have also been studied in PH-LHD. The LEPHT trial demonstrated that riociguat is well tolerated and led to improvements in cardiac index and PVR, though it did not significantly reduce mPAP.[90] Similarly, the DILATE-1 trial in PH-LHD showed that riociguat improved stroke volume and decreased systolic blood pressure without altering heart rate, but it failed to significantly affect mPAP or PVR.[91] The VICTORIA trial with vericiguat in HFrEF demonstrated clinical benefits by reducing the combined endpoint of cardiovascular death and HF hospitalizations, suggesting that its effects may be driven more by improvements in CO than by changes in pulmonary hemodynamics.[92] While sGCs are generally well tolerated, their limited efficacy in reducing pulmonary pressures raises questions about their precise role in PH-LHD and whether their benefits are predominantly driven by systemic effects rather than pulmonary vascular effects. Additionally, in patients unsuitable for ACEi/ARB/ARNI, nitrate therapy serves as an alternative option. However, the contraindication of nitrates with sGCs—due to the risk of excessive vasodilation and hypotension—presents a significant challenge to their application in this group.

Prostacyclin analogs, which possess potent vasodilatory, antithrombotic, and antiproliferative properties, have yielded mixed outcomes in PH-LHD. While epoprostenol improved cardiac index and decreased PAWP, the FIRST trial was terminated early due to increased mortality.[93] The observed excess mortality was attributed to worsening HF, possibly related to vasodilation-induced neurohormonal activation and stimulation of the renin–angiotensin system, leading to fluid retention and hemodynamic instability.[93]

A meta-analysis evaluating multiple PH-targeted therapies (PDE5 inhibitors, prostacyclins, ERAs, and sGCs stimulators) in PH-LHD found that while PDE5 inhibitors may improve exercise capacity, all drug classes were associated with a higher risk of adverse events. This reinforces the WSPH recommendation against using PH-specific therapies in this population.[94]

Devices

The interatrial shunt device (IASD) represents a novel approach aimed at reducing left atrial pressure (LAP) through controlled LA decompression. The goal is to alleviate congestion in patients with HF.[95–97] The REDUCE LAP-HF II trial, a prospective randomized controlled trial involving 626 HFpEF patients with IpcPH and exercise PAWP greater than 25 mm Hg with PVR less than 3.5 WU, compared IASD

implantation with a sham procedure over a 24 month period.[95,96] The study found no significant impact of IASD on the primary composite outcome, which included cardiovascular death, non-fatal ischemic stroke, and total HF events. Given that IASD increases pulmonary blood flow, its effects may vary based on pulmonary vascular remodeling. A secondary analysis by Borlaug and colleagues[97] stratified patients based on latent PVD, defined as peak exercise PVR greater than 1.74 WU. Results indicated worse outcomes in patients with latent PVD, while those without PVD showed potential clinical benefits. These findings suggest that IASD may be beneficial for HFpEF patients with IpcPH but could be harmful to those with CpcPH or latent PVD. Further studies are needed to refine patient selection and determine the long-term efficacy and safety of IASD in patients with PH-LHD.

Pulmonary artery denervation (PADN) is a catheter-based procedure that ablates the innervated regions involved in the baroreceptor reflex in the PA to reduce PH.[98] Preclinical studies suggest that PADN may help restore autonomic balance in PH-LHD by modulating adrenergic receptors.[99] In phase II trials, PADN improved mPAP and 6 min walk distance across various PH subtypes.[100] The PADN-5 trial compared PADN with sildenafil in patients with PH and HF, demonstrating a greater improvement in the 6 min walk distance (83 m vs 15 m, $P<.001$) and a lower PVR with PADN.[98] However, as PADN was compared against sildenafil, which is not approved for PH-LHD, the results remain controversial. In a 3 year outcome study, PADN continued to show benefits, including significant improvements in exercise capacity, cardiac function, and clinical outcomes.[101] While PADN shows potential across multiple PH types, its role in PH-LHD remains investigational, further long-term studies are needed to confirm its safety and clinical benefits in PH-LHD.

In cases of advanced HFrEF, an LVAD can be used as a bridge to transplantation, a bridge to recovery, or destination therapy.[102] By reducing LV pressure, LVAD implantation often leads to lower pulmonary artery pressure and PVR. A retrospective study involving 51 LVAD patients with high PVR showed a significant drop in mPAP from 43 to 22 mm Hg and PVR from 6.3 to 2.2 WU several months after implantation, with sustained benefits observed even after heart transplantation in some patients.[103] Similar findings were reported in a study of 89 LVAD recipients, where PVR normalized within 3 years in all patients, including those with CpcPH.[104] However, not all patients experience full reversal of PH, and up to 43% of LVAD patients had persistent precapillary PH, which was linked to worse survival outcomes[105] (**Fig. 3**).

FUTURE DIRECTIONS

Given the complexity of PH-LHD, the limited efficacy of targeted therapies highlights the need for a shift in research focus toward identifying specific PH-LHD phenotypes that could respond to personalized treatments. For example, patients exhibiting significant RV dysfunction might benefit from PDE5i, whereas those with pronounced pulmonary vascular remodeling may require innovative therapies targeting vascular pathology directly.

Exploring early-stage PH-LHD, prior to the onset of irreversible vascular changes, and testing combination approaches that address both cardiac dysfunction and pulmonary hemodynamics simultaneously could pave the way for more effective interventions. The CADENCE study, a recent clinical trial, exemplifies this approach by investigating the effects of such combined interventions on PH-LHD outcomes, offering preliminary insights into their potential efficacy.[106] Nevertheless, effective management of underlying HF and valvular disease remains the cornerstone of PH-LHD

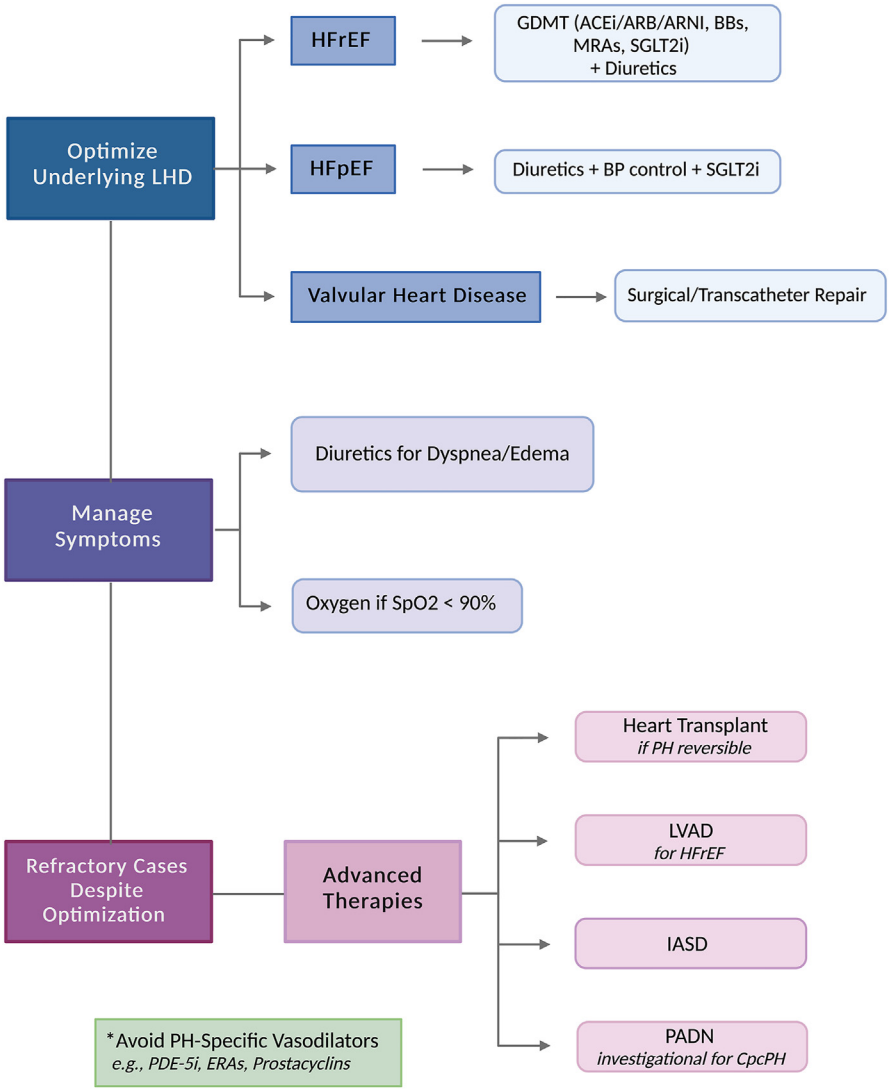

Fig. 3. Management of pulmonary hypertension due to left heart disease. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BBs, beta blockers; ERAs, endothelin receptor antagonists; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IASD, interatrial shunt device; MRAs, mineralocorticoid receptor antagonists; PADN, pulmonary artery denervation; PDE-5i, phophodiessterase-5 inhibitor; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; prostacyclins, prostacyclin analogues or prostacyclin receptor agonists; LVAD, left ventricular assist device; SGLT2i, sodium-glucose contransporter-2 inhibitor.

therapy. Optimizing these conditions is essential to halt disease progression, prevent further deterioration of the right ventricle, and improve patient outcomes.

A crucial step toward advancing research and trial design for PH-LHD is establishing a widely accepted, reproducible definition of the disease, particularly one that

incorporates provocative maneuvers to better differentiate between precapillary and postcapillary components.[6] Additionally, understanding how the chronicity and severity of LHD, along with genetic, epigenetic, and inherited factors, influence the development of combined CpcPH versus IpcPH is essential for refining risk stratification and identifying therapeutic targets.[6]

More robust phenotyping may help identify subgroups that are more likely to benefit from PH-directed therapy, particularly those with CpcPH and significant RV dysfunction. Research has shown that a combination of PVR greater than 5 WU, pulmonary arterial compliance (PAC) less than 1.2 mL/mm Hg, and diastolic blood pressure below 70 mm Hg can predict non-responsiveness to systemic vasodilator therapy in patients with HFrEF.[107] This highlights the importance of incorporating hemodynamic markers into trial design.

A deeper understanding of the pathophysiology and mechanisms underlying PH-LHD is necessary to develop targeted therapies and establish an evidence-based approach for HF patients who develop PH. Identifying the biological pathways and genetic markers associated with PH-LHD will be crucial for advancing personalized treatment approaches.[108] Future clinical trials should focus on proper patient selection based on HF subtype (HFrEF vs HFpEF), PH phenotype (IpcPH vs CpcPH), and degree of RV dysfunction, while ensuring clear and standardized outcome measures, including hemodynamic and clinical endpoints. These refinements will be vital for enhancing therapeutic decision-making and improving outcomes for patients with PH-LHD.

SUMMARY

PH-LHD is a prevalent and clinically significant condition classified as WHO Group 2 PH, arising from elevated LA pressure and left heart dysfunction. The 6th WSPH defines PH as a mPAP greater than 20 mm Hg, measured by RHC. PH-LHD is further divided into IpcPH and CpcPH based on PVR and DPG. Patients with CpcPH exhibit greater RV dysfunction and higher mortality than those with IpcPH due to progressive pulmonary vascular remodeling.

The pathogenesis of PH-LHD is largely driven by LA dysfunction, pulmonary congestion, and endothelial dysfunction. Over time, increased pulmonary venous pressure leads to vascular remodeling, resulting in increased PVR and pulmonary vascular stiffening, particularly in CpcPH. This progression increases RV afterload, leading to RV hypertrophy, dilation, TR, and ultimately RHF. The presence of RV dysfunction in PH-LHD is a major predictor of worse outcomes, underscoring the need for early detection and intervention.

RHC remains the gold standard for PH classification, distinguishing PH-LHD from PAH based on PCWP. However, hemodynamic challenges, including respiratory variation in PAWP, misinterpretation of waveforms, and discrepancies between PAWP and LVEDP can lead to diagnostic errors. Exercise or fluid challenge testing may help differentiate between PH-LHD and precapillary PH, particularly in borderline cases.

Management of PH-LHD centers on optimizing HF therapy rather than targeting PH itself. PAH-specific therapies, including ERAs, phosphodiesterase-5 inhibitors, and prostacyclin analogs, have shown no benefit in PH-LHD and may cause harm.[108] Instead, GDMT for HFrEF, including beta-blockers, ACEi/ARB/ARNI, SGLT2i, MRAs, and diuretics—remains the mainstay of treatment. For HFpEF, key strategies include SGLT2i use, volume management, and blood pressure regulation. In advanced HFrEF cases, LVADs may be employed to lower PVR and enhance pulmonary hemodynamics.

Emerging interventional therapies, such as LASD and PADN, are being investigated for PH-LHD. IASD may provide symptomatic relief in selected HFpEF patients with IpcPH, but its use in CpcPH may worsen outcomes due to increased pulmonary blood flow. PADN has demonstrated early hemodynamic improvements, but long-term safety and efficacy in PH-LHD remain unclear.

Prognosis in PH-LHD depends largely on the presence of CpcPH and RV dysfunction. Patients with PVR greater than 5 WU and PAC less than 1.2 mL/mm Hg exhibit poor responses to vasodilators and worse long-term outcomes. As PH-LHD represents a heterogeneous condition, a phenotype-based approach may improve treatment strategies, helping to identify subgroups that might benefit from PH-specific therapies.

Future research should focus on refining diagnostic criteria, understanding pathophysiologic mechanisms, and developing novel therapeutic approaches. Establishing standardized phenotypic classifications and integrating genetic, metabolic, and hemodynamic markers could aid in patient stratification and personalized therapy.

CLINICS CARE POINTS

- Definition: PH is defined as mPAP greater than >20 mm Hg; PH-LHD (WHO Group 2) is diagnosed when PCWP greater than 15 mm Hg.
- PH-LHD vs PAH: Distinguishing PH-LHD from PAH is critical to prevent inappropriate PAH-targeted therapy.
- CpcPH vs IpcPH: CpcPH is associated with worse functional status and higher mortality.
- Diagnostic testing: Exercise and fluid challenge testing can unmask PH-LHD in patients with borderline hemodynamics.
- Pathophysiology: LA dysfunction drives PH-LHD, causing pulmonary congestion and vascular remodeling.
- Prognostic markers: RV dysfunction and PVR greater than 5 WU predict poor vasodilator response and worse outcomes.
- Disease progression: PH progression leads to RV dilation, TR, systemic congestion, and worsening HF.
- PAWP measurement: PAWP should be taken at end-expiration for accuracy.
- Misclassification risks: Hybrid PA-PAWP tracings may be misleading—check PAWP saturation for confirmation.
- PAWP vs LVEDP: PAWP and LVEDP may not always correlate, especially in AF or mitral regurgitation.
- Therapeutic considerations: PAH-specific therapies (ERAs, PDE5i, prostacyclins) should not be used in PH-LHD due to lack of benefit and potential harm.
- Management strategy: Optimizing heart failure treatment (GDMT) is the cornerstone of PH-LHD management.
- Phenotype-based approach: Phenotype-based approach may improve treatment selection and identify patients who could benefit from targeted PH therapies.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) used ChatGPT and Grammarly to enhance readability and coherence without altering the original content. After using

this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

DISCLOSURES

The authors have nothing to disclose.

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