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POSITION PAPER

A roadmap for therapeutic discovery in pulmonary hypertension associated with left heart failure. A scientific statement of the Heart Failure Association (HFA) of the ESC and the ESC Working Group on Pulmonary Circulation & Right Ventricular Function

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Pulmonary hypertension (PH) associated with left heart failure (LHF) (PH-LHF) is one of the most common causes of PH. It directly contributes to symptoms and reduced functional capacity and negatively affects right heart function, ultimately leading to a poor prognosis. There are no specific treatments for PH-LHF, despite the high number of drugs tested so far. This scientific document addresses the main knowledge gaps in PH-LHF with emphasis on pathophysiology and clinical trials. Key identified issues include better understanding of the role of pulmonary venous versus arteriolar remodelling, multidimensional phenotyping to recognize patient subgroups positioned to respond to different therapies, and conduct of rigorous pre-clinical studies combining small and large animal models. Advancements in these areas are expected to better inform the design of clinical trials and extend treatment options beyond those effective in pulmonary arterial hypertension. Enrichment strategies, endpoint assessments, and thorough haemodynamic studies, both at rest and during exercise, are proposed to play primary roles to optimize early-stage development of candidate therapies for PH-LHF.

Keywords Pulmonary hypertension • Heart failure • Therapy • Translational • Drug

Introduction

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary artery pressure (mPAP) >20 mmHg as measured by right heart catheterization (RHC).[1] The current classification of PH encompasses five groups, differentiated based upon haemodynamic and clinical findings.[2] Group 2 PH is due to left heart disease (LHD), which often results in left heart failure (LHF).

Worldwide, PH associated with LHD (PH-LHD) is the most common type of PH.[3] Albeit the exact prevalence of group 2 PH is not well-defined, non-invasive studies based on echocardiography indicate that it is present in 65% to 85% of subjects with LHD or LHF.[4,5] It is important to note that echocardiography can both over- and underestimate pulmonary artery pressure (PAP),[6] and that a tricuspid regurgitation (TR) jet, upon which the echocardiographic estimate of PH relies, may be absent even in the presence of significant PH.[7] In some patients, PH directly contributes to symptoms and reduced functional capacity, negatively affects right heart function, and eventually dictates a poor prognosis.[8] The impact of PH-LHD is even greater considering the lack of any specific therapy, in sharp contrast with the many options available for pulmonary arterial hypertension (PAH, or group 1 PH) and chronic thromboembolic PH (group 4 PH).

In 2022, the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology (ESC), together with members of the ESC Working Group on Pulmonary Circulation & Right Ventricular Function, held a workshop aimed at discussing the main gaps in knowledge of PH associated with LHF (PH-LHF) pathophysiology and phenotyping, leading to limitations in clinical trial design, and at developing a roadmap to guide research into new treatment modalities. The cumulative outputs of this workshop are presented in this article. PH associated with acute LHF was not specifically addressed, although it purportedly overlaps with PH associated with chronic LHF in many aspects; hence, throughout the document the term PH-LHF refers to PH associated with chronic LHF.

Current status on the definition, pathophysiology, and treatment of pulmonary hypertension associated with left heart failure

Definition

The definition of PH-LHF is haemodynamic and coincides with the one of PH-LHD, being the former a subtype of the latter. The terms 'isolated post-capillary PH' (IpcPH) and 'combined post-capillary and pre-capillary PH' (CpcPH) are used to differentiate between PH merely secondary to the backward transmission of elevated left-sided filling pressures and PH compounded by additional vasoconstriction and/or remodelling of pulmonary vasculature (pulmonary vascular disease [PVD]), respectively.[9] In both forms, pulmonary artery wedge pressure (PAWP) is >15 mmHg, but pulmonary vascular resistance (PVR) is >2 Wood units (WU) only in CpcPH.[1]

Good-quality haemodynamic evaluation with adequate zeroing of the pressure signal is critical to recognize PH-LHD and PH-LHF and distinguish IpcPH from CpcPH.[10] If the PAWP tracing is not satisfactory or the measured value is unexpected, complete balloon occlusion of the pulmonary artery (PA) at the tip of the catheter should be confirmed by measuring oxygen saturation.[11]

Pulmonary artery wedge pressure at rest might be reduced to the normal range despite the presence of heart failure (HF) in response to diuretic administration, or in patients with elevation in PAWP only during stresses, such as exercise in the form of supine or upright cycle ergometry or arm weight lifting.[12]

Provocative challenges may be appropriate in situations of borderline PAWP values and intermediate/high pre-test probability of PH-LHF. Even though exercise testing is commonly utilized at expert centres for this purpose,[12,13] assessment and interpretation of exercise haemodynamics is not universally available. However, recent studies have suggested that PVD that is apparent only during exercise may have clinical relevance.[14] For centres where exercise testing is not feasible, alternatives include the passive leg raise manoeuvre or an acute fluid load (500 ml or 7 ml/kg over 5 min), after which a rise of PAWP to >18 mmHg is considered abnormal and suggestive of pathological elevation of left cardiac filling pressure in response to hypervolaemia.[15–17]

Pathophysiology

Pulmonary hypertension entails an adverse prognosis primarily because of marked increases in afterload on the right ventricle and end-organ damage secondary to right heart failure (RHF).[18]

Pulmonary vascular resistance is a measure of the resistive component of PH. Nonetheless, a pulsatile component of PH also affects right ventricular (RV) loading conditions, and it is quantified by PA compliance (PAC), which is commonly estimated as the ratio between RV stroke volume (SV) and PA pulse pressure. PVR and PAC are inversely and hyperbolically related.[19]

Alterations of both PVR and PAC have been associated with higher mortality in PH-LHD and PH-LHF[20,21]. PVR was also related to RV remodelling and dysfunction,[22] elevated natriuretic peptide levels,[23] and augmented exercise hyperventilation,[24] while lower PAC was associated with a lower ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic PAP (sPAP) on echocardiography.[22,25] Even patients with LHF, preserved ejection fraction and normal or mildly increased mPAP at rest have lesser decrease in PVR and greater reduction in PAC during exercise than controls, alongside inadequate RV reserve and impaired exercise capacity.[26] Interestingly, sex differences may exist, as women with PH-LHD and PH-LHF display a more favourable pattern of RV adaptation to afterload than men.[27–30]

While elevated PVR has traditionally been associated with vasoconstriction and remodelling in the pulmonary arterial (pre-capillary) circulation, it is now apparent that PH-LHD also entails pulmonary venous (post-capillary) remodelling[31,32] (*Figure 1*). Indeed, subjects with CpcPH display more dramatic increases in lung congestion during exercise than those with IpcPH, despite the same PAWP, suggesting greater increases in capillary

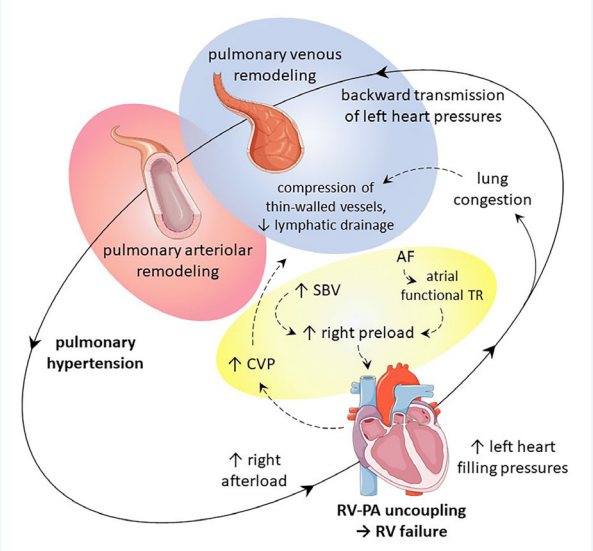

Figure 1 Schematic representation of the pathophysiology of pulmonary hypertension (PH) associated with left heart failure (PH-LHF). PH-LHF is initiated by the backward transmission of elevated left cardiac filling pressures to the pulmonary circulation, so called post-capillary component of PH-LHF (highlighted in light blue). In some individuals, pulmonary arteriolar remodelling superimposes, causing a rise in vascular resistance that compounds PH (pre-capillary component, light red). Sustained pulmonary congestion may contribute to the post-capillary component of PH via thickening of the pulmonary interstitium, and right heart congestion via impaired alveolar fluid clearance and lymphatic drainage. Enhanced stress blood volume (SBV) and atrial fibrillation (AF) are additional factors precipitating right heart overload (yellow). Structural remodelling also occurs in pulmonary veins and capillaries, and it is now debated whether and to which extent it contributes to the increase in pulmonary vascular resistance. CVP, central venous pressure; PA, pulmonary artery; RV, right ventricle; TR, tricuspid regurgitation.

pressure related to venous disease, but also left ventricle/right ventricle interactions during exercise.[33] These patients also display more severe limitations in aerobic capacity due to cardiac output (CO) impairment, which in turn are caused by abnormalities in exertional RV-PA coupling, pericardial restraint, and inadequate pulmonary vasodilatation and vascular recruitment.[33,34]

Accumulation of interstitial lung water in HF is the sum of increased hydrostatic pressure, increased capillary permeability, and reduced alveolar fluid clearance and lung lymphatic drainage[35] due to high central venous pressure.[36] Prolonged pulmonary congestion promotes fibrosis of the interstitial space[37] and capillary remodelling.[38] Independent of left atrial pressure, water accumulation in perivascular spaces and in the lymphatics of the lung causes the compression of the thin-walled pulmonary vessels, with a further increase in PVR and decrease in PAC[39] (*Figure 1*). Reversal of these alterations is attained by decongestion.[40,41]

Afterload-independent factors may precipitate or promote RHF in PH-LHF. In LHF with reduced ejection fraction, three-dimensional longitudinal and anteroposterior shortening of the right ventricle was correlated with left ventricular (LV) systolic dysfunction, reflecting the interdependence between the failing left ventricle and the right ventricle, with a realignment of forces resulting in increased radial RV shortening.[42,43]

In HF with preserved ejection fraction (HFpEF), atrial fibrillation (AF) may lead to RHF in a preload- rather than afterload-dependent manner[30,44,45] by causing volume overload, atrial remodelling and atrial functional TR.[46] Interestingly, it is now debated whether TR may contribute to the CpcPH profile, being associated with reduced anterograde pulmonary blood flow, pulmonary vascular de-recruitment, and a mild increase in PVR.[47,48]

Treatment

Treatment of volume overload with diuretics lessens the severity of PH-LHF, and prompt up-titration of diuretics upon detection of an asymptomatic rise in PAP by a sensor implanted in the PA (CardioMEMS) reduced HF events in North American patients in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) and the haemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trials.[49,50] PAP lowering and prevention of HF events by PAP-guided HF therapy were found irrespective of the presence of IpcPH or CpcPH.[51] More recently, haemodynamic monitoring with CardioMEMS was also shown to lead to better quality of life and less HF hospitalizations in European subjects with HF.[52]

Heart failure with reduced ejection fraction (HFrEF) pharmacotherapy also reduces PAP[53,54] (online supplementary *Table S1*), and improvement in pulmonary haemodynamics has been reported after transcatheter repair of functional mitral regurgitation in HFrEF.[55,56]

Not surprisingly, implantation of a LV assist device (LVAD) appears to be the most effective way to diminish or eliminate PH in HFrEF. In an analysis of the Interagency Registry for Mechanically Assisted Circulatory Support including 1581 patients with baseline PVR ≥3 WU, PVR decreased rapidly over the first 3 months after LVAD implantation, and more gradually thereafter. Nevertheless, 15–25% of patients had PVR persistently ≥3 WU 36 months after LVAD implantation.[57] In this context, decoupling between diastolic PAP and PAWP was identified as a prognostic factor after LVAD implantation.[58]

Hence, the assumption that optimal treatment of LHF will lead to disappearance of PH-LHF may be too simplistic, and there is a strong rationale to investigate therapeutic interventions specifically targeting PVD in PH-LHF. So far, most experience comes from attempts to treat PH-LHD, including but not limited to PH-LHF, with drugs used for PAH.

Clinical trials evaluating PAH targeted pathways in PH-LHD are summarized in *Table 1*. Not only approved PAH medications, but also compounds that are still under investigation in PAH have been assessed for PH-LHD, such as fasudil, a rho-kinase inhibitor. Out of 34 studies, 10 (29.4%) were concluded and met the primary efficacy hypothesis. Overall, there were no clear signals of efficacy and some concerns for safety, generating more questions than answers.

It is commonly argued that the subjects enrolled in these trials had a variable degree of PVD. In some cases, RHC was not even required for recruitment. Therefore, the response to PAH medical therapy, which primarily acts on pulmonary arterioles, varied. In fact, pulmonary arteriolar vasodilators may be paradoxically detrimental in patients with PH-LHD and, particularly, PH-LHF, by worsening lung congestion via increased pulmonary blood flow and, thus, hydrostatic pressure in pulmonary capillaries.[59] Based on this reasoning, it was anticipated that PAH medications would be beneficial if selectively prescribed for RHC-proved CpcPH, though this prediction would be tempered by the relative contribution of elevated PAWP to PH.

A case in point is the Macitentan in subjects with combined prE- and post-capiLlary pulmOnary hypertension due to left ventricular DYsfunction (MELODY-1) randomized controlled trial (RCT), in which the endothelin receptor antagonist (ERA), macitentan, led to more fluid retention than placebo, with no significant changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations or in pulmonary haemodynamics in patients with CpcPH, as determined by RHC.[60] Despite this, the Study to Evaluate Whether Macitentan is an Effective and Safe Treatment for Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease (SERENADE) was conducted in subjects with symptomatic LHF, RHC evidence of PVD, and no fluid retention or HF decompensation following treatment with placebo and macitentan during a run-in phase. Although this RCT was terminated prematurely because of slow enrolment, no difference was observed between the two arms in NT-proBNP levels at follow-up, as well as in time to worsening HF, quality of life, and physical activity as measured by accelerometer. Moreover, oedema/fluid retention and adverse cardiac events were more frequent with macitentan than placebo (Voors A.A., Heart Failure Congress 2022, unpublished data).

Trials evaluating drugs acting on the nitric oxide (NO) pathway have yielded seemingly conflicting results. While the phosphodiesterase-5 inhibitor (PDE5i), sildenafil, ameliorated haemodynamics and exercise capacity in PH-HFrEF in early investigations,[61–63] other studies including the Sildenafil in Heart Failure

Table 1 Clinical trials evaluating pulmonary arterial hypertension drugs for treatment of pulmonary hypertension associated with left heart disease and left heart failure

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. patients/type	PH definition for inclusion	Primary and secondary outcomes	Main results
Califf, 1997 FIRST[1]	Epoprostenol 2 ng/kg/min → dose-limiting AE vs. standard care IV	Multicentre, randomized, open-label	LVEF <25%, or <30% but recently treated with IV inotrope	CI ≤2.2 L/min/m^2 and PAWP ≥15 mmHg at RHC RHC data: yes	Primary: overall survival Secondary: clinical events, congestive HF symptoms, 6MWD, and quality-of-life measures	Terminated early because of a strong trend toward decreased survival in patients treated with epoprostenol
Alaeddini, 2004[2]	Sildenafil 25 mg or 50 mg up to every 8 h Oral	Single-centre, randomized, open-label/1 day	$n = 14$/LVEF ≤35%	mPAP >25 mmHg at RHC RHC data: yes	Changes in haemodynamic parameters	Reduction in mPAP, PAWP, PVR and systemic vascular resistance NS increase in CO, but significant increase in CI NS differences in systemic BP
Lewis, 2007, NCT00309790[3]	Sildenafil 25 to 75 mg (mean 49 ± 6 mg) tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/12 weeks	$n = 34$/LVEF <40%	mPAP >25 mmHg at RHC RHC data: yes	Changes in TTE parameters, NT-proBNP levels, exercise capacity assessed by 6MWD and CPET, haemodynamic parameters, quality of life as assessed by the MLHFQ	Reduction in PVR, increase in CO NS difference in PAWP and mPAP Improvement in exercise capacity and quality of life
Kaluski, 2008[4]	Bosentan 8–125 mg bid (mean daily dose 55.6 ± 34.1 mg) vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/20 weeks	$n = 94$/LVEF <35%	sPAP >40 mmHg at TTE RHC data: no	Primary: change in sPAP Secondary: change in CI	NS differences in clinical or haemodynamic parameters Higher rates of AE requiring drug discontinuation
Bahler, NCT00781508	Sildenafil 50 mg/day vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/single dose administration	$n = 10$/LVEF cutoff not specified	Previously documented PAP >40 mmHg RHC data: not specified	Primary: changes in E/e' ratio Secondary: changes in 6MWD	Completed in 2009 Results from ClinicalTrials.gov: NS differences in primary and secondary outcomes
BOSMIVAR, NCT01270750	Bosentan 62.5 mg bid → 125 mg bid Oral	Single-centre, non-randomized, open-label/6 months	Target $n = 10$/congestive HF WHO-FC IIIB/V due to non-operable rheumatic mitral stenosis	mPAP >40 cmH_2O RHC data: not specified	Primary: changes in 6MWD and peak VO_2 at CPET Secondary: changes in TTE-estimated peak and mean pulmonary pressure and LVEF; changes in NT-proBNP levels; changes in Borg dyspnoea index	Status unknown Last update in 2011
Guazzi, 2011, NCT01156636[5]	Sildenafil 50 mg tid vs. placebo Oral	Two-centre, randomized, double-blind, placebo-C/1 year	$n = 44$/LVEF ≥50%	sPAP >40 mmHg at TTE RHC data: yes	Primary: change in pulmonary haemodynamics Secondary: changes in clinical, TTE, RHC, quality of life, and lung function parameters	Improvement in sPAP and pulmonary arteriolar resistance, RV function, LV relaxation and distensibility, lung interstitial water
Guazzi, 2012[6]	Sildenafil 50 mg tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/1 year	$n = 32$/LVEF <45%	mPAP 25–35 mmHg at RHC RHC data: yes	Changes in haemodynamic and CPET parameters, exercise oscillatory breathing, and quality of life as assessed by a 16-item questionnaire	In patients with exercise oscillatory breathing, sildenafil improved functional capacity and modulated the exercise breathing pattern, and improved PAP, CO, PVR, and TPG
Bonderman, 2013, LEPHT, NCT01065454[7]	Riociguat 0.5, 1 or 2 mg tid vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/16 weeks	$n = 201$/HFrEF	mPAP ≥25 mmHg at RHC RHC data: yes	Primary: changes in mPAP Secondary: changes in haemodynamic and TTE parameters Exploratory: composite of the incidence of clinical worsening, the dual composite of incidence of CV death or hospitalization, quality of life (as assessed by EURO-Qol5DQ and MLHFQ), WHO-FC, 6MWD, and NT-proBNP	Primary endpoint not met in the 2 mg group: NS difference in mPAP, but increase in stroke volume index and CI, reduction in PVR and systemic vascular resistance, reduction in MLHFQ score

Table 1 (Continued)

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. patients/type	PH definition for inclusion	Primary and secondary outcomes	Main results
HEARTWORK, NCT01065051	Riociguat 1 mg tid vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/single dose administration	LV systolic dysfunction	PH due to LV systolic dysfunction RHC data: yes	Primary: changes in peak power index at rest[a] Secondary: changes in LV stroke work index, LVEF, end-systolic elastance at rest; changes in peal power index during CPET; changes in lateral mitral annular peak systolic velocity, peak systolic tricuspid annular velocity, E' wave and TAPSE during CPET; changes in ventilatory efficiency from baseline to anaerobic threshold during CPET	Terminated in 2014 No results published; 1 patient enrolled in ClinicalTrials.gov
LV strain, NCT01800292	Sildenafil 20 mg tid Oral	Single-centre, open-label, single-group/3 months	$n = 9$/LVEF ≥50%	mPAP >25 mmHg, PAWP >15 and ≤18 mmHg, PVR >3 WU at RHC RHC data: yes	Primary: changes in 6MWD Secondary: changes in TTE parameters, WHO-FC, and BNP levels	Completed in 2014 No results available
PITCH-HF, NCT01910389	Tadalafil 40 mg/day vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/18 months (maximum follow-up of 3 years)	$n = 23$/LVEF <40%	Documented PH history within 6 months prior to enrolment RHC data: not specified	Primary: composite of CV mortality and HF-related hospitalization Secondary: CV death; HF-related hospitalization; all-cause mortality; composite outcome of all-cause mortality and CV hospitalization; changes in 6MWD; changes in quality of life as assessed by MLHFQ	Prematurely terminated in 2014 23 patients enrolled
PITCH-ER, NCT01960153	Tadalafil 40 mg/day vs. placebo Oral	Phase III, multicentre, randomized, double-blind, placebo-C/48 weeks	$n = 23$/LVEF <40%	Documented PH history within 6 months prior to enrolment/haemodynamic data: not specified	Primary: changes in renal function; incidence of acute kidney injury Secondary: changes in renal function and incidence of acute kidney injury stratified by diabetes presence	Withdrawn in 2017
Bonderman, 2014, DILATE-1, NCT01172756[8]	Riociguat 0.5, 1 or 2 mg in three subsequent ascending dose cohorts vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/single dose administration	$n = 36$/LVEF <50%	mPAP ≥25 mmHg and PAWP >15 mmHg at RHC RHC data: yes	Primary: changes in mPAP Secondary: haemodynamic and TTE parameters, biomarker levels, safety and pharmacokinetics	2 mg dose: amelioration of stroke volume, reduction in systolic BP and RV end-diastolic area NS differences in mPAP PAWP, PVR, and TPG
Kim, 2015, ULTIMATE-SHF, NCT01646515[9]	Udenafil 50 mg→ 100 mg bid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/12 weeks	$n = 41$/LVEF ≤40%	sPAP ≥40 mmHg at TTE, but this was not a mandatory inclusion criterion RHC data: no	Primary: changes in peak VO_2 at CPET Secondary: changes in VE/VCO_2 slope at CPET; changes in LVEF and diastolic function; changes in post-exercise sPAP at stress TTE; changes in WHO-FC and BNP; all-cause mortality; hospital admission for HF	Improvement in peak VO_2 Decrease in VE/VCO_2 slope, improvement in TTE measurements including post-exercise sPAP, improvement in WHO-FC
Hoendermis, 2015, NCT01726049[10]	Sildenafil 60 mg tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/12 weeks	$n = 52$/LVEF ≥45%	mPAP >25 mmHg and PAWP >15 mmHg at RHC RHC data: yes	Primary: changes in mPAP Secondary: changes in PAWP, CO, peak VO_2 and exercise capacity by CPET	NS differences in mPAP and other haemodynamic or clinical parameters
Koller, 2017, BADDHY, NCT00820352[11]	Bosentan 62.5 mg bid for 4 weeks → 125 mg bid for 8 weeks vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/12 of treatment +12 of follow-up	$n = 20$/LVEF ≥50%	mPAP >25 mmHg and PAWP >15 mmHg at RHC RHC data: not specified	Primary: changes in 6MWD after 12 weeks Secondary: change in 6MWD at 24 weeks; changes in haemodynamics as assessed by TTE; clinical worsening; quality of life	No significant differences in 6MWD Significant reduction in sPAP and right atrial pressure as assessed by TTE in the placebo group
Liu, 2017, NCT01726049[12]	Sildenafil 60 mg tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/12 weeks	$n = 52$/LVEF ≥45%	mPAP >25 mmHg and PAWP >15 mmHg at RHC RHC data: yes	Changes in cardiac structure and function by TTE, in CPET, and in quality of life as assessed by KCCQ	NS differences in cardiac structure and function, integrative exercise responses, laboratory parameters, and quality of life

Table 1 (Continued)

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. patients/type	PH definition for inclusion	Primary and secondary outcomes	Main results
Guglin, Sildenafil-HF, NCT02304705	Sildenafil 20 mg tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/90 days	$n = 33$/any LVEF	mPAP >25 mmHg, PAWP >15 mmHg and PVR >3 WU at RHC RHC data: yes	Primary: changes in 6MWD Secondary: changes in TAPSE, CO and CI, PVR, and BP	Terminated in 2017 Unpublished results (33 patients enrolled, but only 22 had outcome data collected)
Ryu, NCT01913847	Sildenafil 20 mg tid vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C/12 weeks	Target $n = 144$/LVEF ≤40%	sPAP ≥40 mmHg RHC data: not specified	Primary; changes in 6MWD Secondary: changes in sPAP, NT-proBNP, WHO-FC, quality of life; time to first occurrence of CV events	Status unknown Last update in 2017
Rosenkranz and Hoeper, PASSION, EudraCT 2017–003688-37	Tadalafil 40 mg/day vs. placebo Oral	Phase III, multicentre, randomized, double-blind, placebo-C/24 weeks	Target $n = 356$/LVEF ≥50%	mPAP ≥25 mmHg, PAWP >15 mmHg PVR >3 WU RHC data: yes	Primary: time to all-cause mortality and HF-related hospitalizations Secondary: cumulative number of CV deaths and total HF hospitalizations; clinical response defined as absence of death or hospitalization, improvement in WHO-FC and/or 6MWD; time from randomization to clinical worsening; changes in NT-proBNP and quality of life; net benefit (proportion of patients with improvement in WHO-FC and/or 6MWD vs. proportion of patients with clinical worsening); health economic impact; safety assessment	Prematurely terminated 123 patients enrolled
Zhang, 2018, ChiCTR-INR-16009511[13]	Fasudil 30 mg bid IV	Two-centre, single-arm, open-label/2 weeks	$n = 58$/LVEF ≥50%	mPAP ≥25 mmHg and PAWP >15 mmHg at RHC RHC data: yes	Changes in WHO-FC, 6MWD, TTE parameters, NT-proBNP and other laboratory tests	Reduction of sPAP in reactive PH Improvement in 6MWD and NT-proBNP in both passive and reactive PH
Vachiéry, 2018, MELODY-1, NCT02070991[14]	Macitentan 10 mg/day vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/12 weeks	$n = 63$/LVEF ≥30%	mPAP ≥25 mmHg, PAWP >15 mmHg and <25 mmHg, DPG ≥7 mmHg and PVR ≥3 WU at RHC RHC data: yes	Primary: composite of significant fluid retention or worsening in WHO-FC Exploratory: changes in NT-proBNP, changes in haemodynamic variables	Higher incidence of fluid retention in the macitentan group Higher incidence of AE and SAE in the macitentan group NS differences in PVR, mean right atrial pressure, PAWP
TDE-HF-301, NCT03037580	Treprostinil 0.125 mg tid → maximum 6 mg tid vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/28 weeks	$n = 84$/LVEF ≥45%	Diagnosis of PH by RHC within 180 days of baseline RHC data: not specified	Primary: changes in 6MWD Secondary: change in NT-proBNP, number of subjects with first clinical worsening, changes in WHO-FC	Terminated in 2019 due to low enrolment
TDE-HF-302, NCT03043651	Treprostinil 0.125 mg tid → maximum 6 mg tid Oral	Multicentre, open-label extension of TDE-HF-301/8 years	$n = 48$//LVEF ≥45%	Same as for TDE-HF-301	Primary: long-term safety of oral treprostinil in subjects who completed TDE-HF-301 Secondary: effects on 6MWD, Borg dyspnoea scale, WHO-FC, and NT-proBNP	Terminated in 2019 due to low enrolment
Belyavskiy, 2020[15]	Sildenafil 25 mg tid for 3 months → 50 mg tid for 3 months Oral	Single-centre, prospective, case–control/6 months	$n = 50$/LVEF >50%)	sPAP >40 mmHg, PVR >3 WU and/or TPG >15 mmHg at TTE and/or RHC RHC data: no	Primary: changes in 6MWD Secondary: changes in WHO-FC, exercise duration and maximal achieved workload during cycle ergometry, mitral E/e' ratio and sPAP both at rest and during diastolic stress, LV and RV structure and function, NT-proBNP	Improvement in exercise capacity, pulmonary haemodynamic parameters, and RV function

Table 1 (Continued)

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. patients/type	PH definition for inclusion	Primary and secondary outcomes	Main results
Frantz, 2021, SOPRANO, NCT02554903[16]	Macitentan 10 mg/day vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/12 weeks	$n = 56$/LVAD implanted within 90 days prior randomization	mPAP ≥25 mmHg, PAWP ≤18 mmHg and PVR >3 WU at RHC RHC data: yes	Primary: changes in PVR Secondary: changes in PAWP, RAP, mPAP, CI, total pulmonary resistance, mixed venous oxygen saturation; changes in NT-proBNP and WHO-FC	Reduction in PVR and TPG NS differences in changes in PAWP and rates of AE
Sun, 2021[17]	Beraprost 40 μg tid plus sildenafil 20 mg tid vs. beraprost 40 μg tid Oral	Single-centre, randomized, double-blind, placebo-C/3 months	$n = 80$/HFmrEF and HFrEF (mean LVEF 41.3 ± 1.6%)	Prior diagnosis of PH with mPAP ≥25 mmHg at rest and ≥30 mmHg during exercise RHC data: not specified	Changes in serum levels of different biomarkers (urotensin II, BNP, vascular endothelin and TNF-α), and changes in TTE parameters	Improvement in PAP, alleviation of HF, increase in LVEF, SV and CO by echo, and improvement in BNP and inflammatory biomarker (TNF-α) in the beraprost + sildenafil group
2022, SERENADE, NCT03153111	Run-in[b] →macitentan 10 mg/day vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/minimum follow-up 24 weeks, maximum follow-up 1 year	Target $n = 300$/LVEF ≥40%	Peak TRV >2.8 m/s or sPAP >40 mmHg and RV dysfunction (TAPSE <17 mm, RV FAC <35%, or RV s' <9.5 cm/s) (TTE) or mPAP ≥25 mmHg, DPG >5 mmHg, or PVR >3 WU (RHC) RHC data: not specified	Primary: changes in NT-proBNP after 24 weeks Secondary: changes in KCCQ clinical summary score, change in accelerometer-assessed proportion of time spent in light to vigorous physical activity after 24 weeks; time to worsening HF over 52 weeks	Prematurely stopped due to slow enrolment (143 patients recruited after successful run-in) NS differences in the study endpoints More oedema/fluid retention, anaemia, and cardiac AE in the macitentan group
2022, SERENADE-OL, NCT03714815	Macitentan 10 mg/day vs. placebo Oral	Multicentre, long-term, open-label extension of SERENADE	$n = 91$/LVEF ≥40%	Same as for SERENADE	Primary: number of all-cause mortality up to 30 days after study treatment discontinuation Secondary (all up to 30 days after study treatment discontinuation): number of all-cause hospital admission; number of patients with treatment-emergent AE and treatment-emergent SAE; changes in BP, pulse rate and body weight; number of patients with treatment-emergent marked laboratory abnormalities	Terminated in 2022 following the results of SERENADE No unexpected/new safety findings
Cooper, 2022, SilHF[18]	Sildenafil 40 mg tid vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/24 weeks	$n = 69$/LVEF ≤40%	sPAP ≥40 mmHg at TTE RHC data: no	Co-primary: improvement in patient global assessment by visual analogue scale and 6MWD	NS differences in quality of life or 6MWD NS differences in sPAP Higher rates of AE
Dachs, 2022, haemoDYNAMIC, NCT02744339[19]	Riociguat up to 1.5 mg tid vs. placebo Oral	Multicentre, randomized, double-blind, placebo-C/26 weeks	$n = 114$/LVEF ≥50%	mPAP ≥25 mmHg and PAWP >15 mmHg at RHC RHC data: yes	Primary: changes in CO at rest Secondary: changes in PVR, systemic vascular resistance, TPG, PAWP, and NT-proBNP; improvement in ≥1 WHO-FC. Exploratory analysis on 6MWD and quality of life as assessed by EURO-QoI5DQ and the MLHFQ	Increase in CO More dropouts due to drug-related AE in the riociguat arm No severe AE or deaths
Howlett, REVAD, NCT03356353	Sildenafil 40 mg tid Oral	Multicentre, single-arm, open-label/55 days	Target $n = 24$/HFrEF requiring LVAD	Central venous pressure/PAWP ratio ≥0.63; pre-operative PVR ≥3 WU RHC data: yes	Primary: PVR reduction Secondary: time to right HF; time to inotrope requirement; time to ICU admission; time to hospitalization; all-cause mortality; drug interruption; worsening in renal function; symptomatic hypotension	Ongoing

Table 1 (Continued)

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. patients/type	PH definition for inclusion	Primary and secondary outcomes	Main results
CADENCE, NCT04945460	Sotatercept 0.3 to 0.7 mg/kg SC	Multicentre, randomized, double-blind, placebo-C/48 weeks	Target $n = 150$/LVEF ≥50%	mPAP >20 mmHg, PAWP >15 mmHg but <30 mmHg, and PVR ≥4 WU at RHC RHC data: yes	Primary: changes in PVR Secondary: change in 6MWD, number of clinical worsening events (hospitalization, administration of IV diuretics, all cause-death, decrease in 6MWD ≥15%), time to clinical worsening, changes in TTE and RHC parameters, changes in NT-proBNP, Borg scale, and WHO-FC	Ongoing

The trials are listed in chronological order and colour-coded as follows: green, primary endpoint met; white, primary endpoint not met; gray, prematurely interrupted or not concluded; red, signal for safety concerns in the intervention arm. The relevant references are provided in online supplementary *Appendix S1*.

6MWD, 6-min walking distance; AE, adverse event; bid, bis in die (twice a day); BNP, B-type natriuretic peptide; BP, blood pressure; CI, cardiac index; CO, cardiac output; CPET, cardiopulmonary exercise testing; CV, cardiovascular; DPG, diastolic pressure gradient; EURO-Qol5DQ, EURO 5-dimension quality of life questionnaire; FAC, fractional area change; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; mPAP, mean pulmonary artery pressure; NCT, identifier number on ClinicalTrials.gov; NS, non-significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; placebo-C, placebo controlled; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricular; s', tissue Doppler s' velocity; SAE, serious adverse event; SC, subcutaneous; sPAP, systolic pulmonary artery pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TID, ter in die (three times a day); TNF-α, tumour necrosis factor alpha; TPG, transpulmonary gradient; TRV, tricuspid regurgitation velocity; TTE, transthoracic echocardiography; VE/VCO$_2$, minute ventilation/carbon dioxide production; VO$_2$, oxygen consumption; WHO-FC, World Health Organization functional class; WU, Wood units.

[a]Peak power index was calculated as (mean systolic arterial pressure − PAWP mean) × CO × (16.667/LV end-diastolic volume).

[b]Eligible patients underwent a sequential run-in phase, during which they took placebo for 4 weeks and then macitentan 10 mg/day for 5 weeks, in order to identify those susceptible to treatment-related AE. Run-in failure, causing exclusion from randomization, was defined as: study treatment compliance <80%; decrease in haemoglobin by >50 g/L from screening or <80 g/L, or need for transfusion; significant fluid retention/worsening of HF; or any AEs that preclude continuation based on investigator's judgment.

(SilHF) trial (which was terminated prematurely) failed to meet any clinically meaningful endpoint signal.[64] The primary endpoint of lowering mPAP versus placebo was not reached either by the Study to Test the Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Systolic Dysfunction (LEPHT) with the soluble guanylate cyclase stimulator, riociguat. However, riociguat significantly improved CO and PVR as compared with placebo.[65]

In PH-HFpEF, two small RCTs were conducted with sildenafil: Hoendermis *et al.*[66] found no improvement of haemodynamics or clinical measures in patients displaying predominantly an IpcPH profile, whereas Guazzi *et al.*[67] did show improvements of haemodynamics and RV function in patients with CpcPH characteristics. In the recent Riociguat in Pulmonary Hypertension and Heart Failure with Preserved Ejection Fraction haemoDYNAMIC Trial (DYNAMIC), 26-week treatment with riociguat led to significantly higher CO and lower mPAP and PVR as compared with placebo in subjects with PH-HFpEF.[68]

Based on available evidence, the 2022 ESC/European Respiratory Society guidelines on PH do not provide a recommendation for or against the use of PDE5i in HFpEF with CpcPH, but recommended against their use in HFpEF and IpcPH.[1] Additional data are awaited from ongoing RCTs, such as PASSION (EudraCT 2017−003688-37).

The activin signalling inhibitor, sotatercept, which consists of the extracellular domain of the human activin receptor type IIA fused to the Fc domain of human immunoglobin G1 (IgG1) and recently proved effective in PAH,[69,70] is currently being investigated in HFpEF and CpcPH in the Study of Sotatercept for the Treatment of Cpc-PH Due to HFpEF (CADENCE, NCT04945460).

It is possible that PAH drugs trigger neurohormonal responses that exacerbate LHF, especially when systemic vascular effects also occur. This could be one of the reasons why the Flolan International Randomized Survival Trial (FIRST) was unsuccessful.[71] In FIRST, the prostacyclin analogue, epoprostenol, acutely and significantly increased cardiac index (CI) and decreased mPAP, PAWP, PVR, and systemic vascular resistance as compared with placebo in patients with severe HFrEF and PH, but was associated with a trend towards shorter 6-min walk distance (6MWD), no improvement in dyspnoea and quality of life, and more deaths than placebo in the long term.[71]

Finally, most trials utilizing PAH therapies in HFpEF were not enriched for subjects at highest risk of RV dysfunction and failure.[72]

The need to improve phenotyping of pulmonary hypertension associated with left heart failure

It has become increasingly clear that a particular patient may belong to more than one PH group because of the presence of different conditions. This is exemplified by the case of systemic sclerosis (SSc), in which the prevalence of PH can be as high as 12−14%.[73] SSc may be associated with a more vascular disease resulting in group 1 PH/PAH, particularly in the limited form of the disease and with positive anticentromere antibodies, or it may entail pulmonary

parenchymal disease with group 3 PH when it is diffuse and with Scl-70 antibody profile. As SSc patients tend to be older and may have intrinsic myocardial dysfunction,[74] LV systolic or especially diastolic dysfunction may alternatively be the underlying cause of or at least contribute to their PH.

Similarly, PH-LHF may include many phenotypes, which respond differently to treatments to the point that, in principle, a certain drug may be very effective in a PH-LHF subgroup and, in contrast, harmful in another one. Clearly, the overall effect of such a medication will be neutral at best, if it is used indiscriminately in the broad PH-LHF population.

Therefore, deep phenotyping of PH-LHF is a prerequisite for therapeutic discovery (*Table 2*).

Clinical features

Within the PH-LHF category, a first subclassification is a consequence of the fact that LHF comprises HFrEF, HF with mildly reduced ejection fraction, HFpEF, and HF secondary to specific cardiac diseases such as valvular heart disease or infiltrative cardiomyopathy (e.g. cardiac amyloidosis). The pathophysiology of PH-LHF is not necessarily the same across these types of LHF.

Moreover, contemporary LHF patients typically have comorbidities that can induce PH in and of themselves or promote it (*Figure 2*).

Chronic obstructive pulmonary disease is the most frequent aetiology of group 3 PH, but it is also found in up to 20% of subjects with LHF.[75] The true prevalence of this respiratory disease could be even higher, since spirometry is highly underused by HF physicians[76] and LHF may also induce restrictive and obstructive spirometric abnormalities, as well as reductions in the diffusing capacity of carbon monoxide (DL_{CO}).[33,36,77–79] Recent data indicate that 10–25% of patients with HFpEF, even with completely normal spirometry, display at least low grade hypoxaemia during exercise. These subjects were found to have more severe pulmonary haemodynamic perturbations, with greater ventilation–perfusion mismatch and physiologic shunt fraction.[80]

When LHF and other aetiologies of PH coexist, it becomes difficult to disentangle their relative role and determine whether LHF is the main determinant of PH. For instance, it was shown

Table 2 Key methods to improve phenotyping of patients with pulmonary hypertension associated with left heart failure

Methodology	Measurement(s)	Information obtained
Pulmonary function testing	DL_{CO}	Lung congestion, pulmonary vascular remodelling
Exhaled breath analysis	Mass spectrometry of exhaled breath	Demonstration of volatile compounds specific of/enriched in HF
Imaging		
Echocardiography, CMR	RV strain	RV-PA coupling
Chest radiography	Congestion scores	Pulmonary congestion
Ultrasonography of the lung	B-lines	Pulmonary congestion
HRCT of the lung	(AI-based) quantification of pulmonary interstitium	Pulmonary congestion
CT pulmonary angiography, including dual-energy CT	Visual and automated analysis of contrast agent distribution	Lung perfusion
Ventilation–perfusion scintigraphy	Visual and automated analysis of tracer distribution	Ventilation–perfusion matching
RHC	RV and PA pressures, maximal isovolumic RV pressure	RV-PA coupling
RHC + CMR, SPECT, or 3D echocardiography	RV and PA pressures, RV volumes	RV-PA coupling
Conductance (pressure–volume) catheterization	RV and PA pressures, RV pressures and volumes	RV-PA coupling
Remote PA monitoring + imaging	PA pressures, RV volumes	RV-PA coupling
RHC with volume challenge	Haemodynamic parameters at rest and after saline infusion	Haemodynamic response to volume overload
RHC during exercise	mPAP/CO, other haemodynamic parameters	Haemodynamic response to exercise
Remote PAP monitoring with implantable PAP sensors (e.g. CardioMEMS)	PAP	PA changes in different settings and over time
Computational methods	SBV	Venous blood distribution

The table summarizes key methods to improve phenotyping of pulmonary hypertension associated with left heart failure patients, which may not be already part of the routine diagnostic evaluation.
3D, three-dimensional; AI, artificial intelligence; CMR, cardiac magnetic resonance; CO, cardiac output; CT, computed tomography; DL_{CO}, diffusing capacity of carbon monoxide; HF, heart failure; HRCT, high-resolution computed tomography; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAP, pulmonary artery pressure; RV, right ventricular; RHC, right heart catheterization; SBV, stressed blood volume; SPECT, single-photon emission computed tomography.

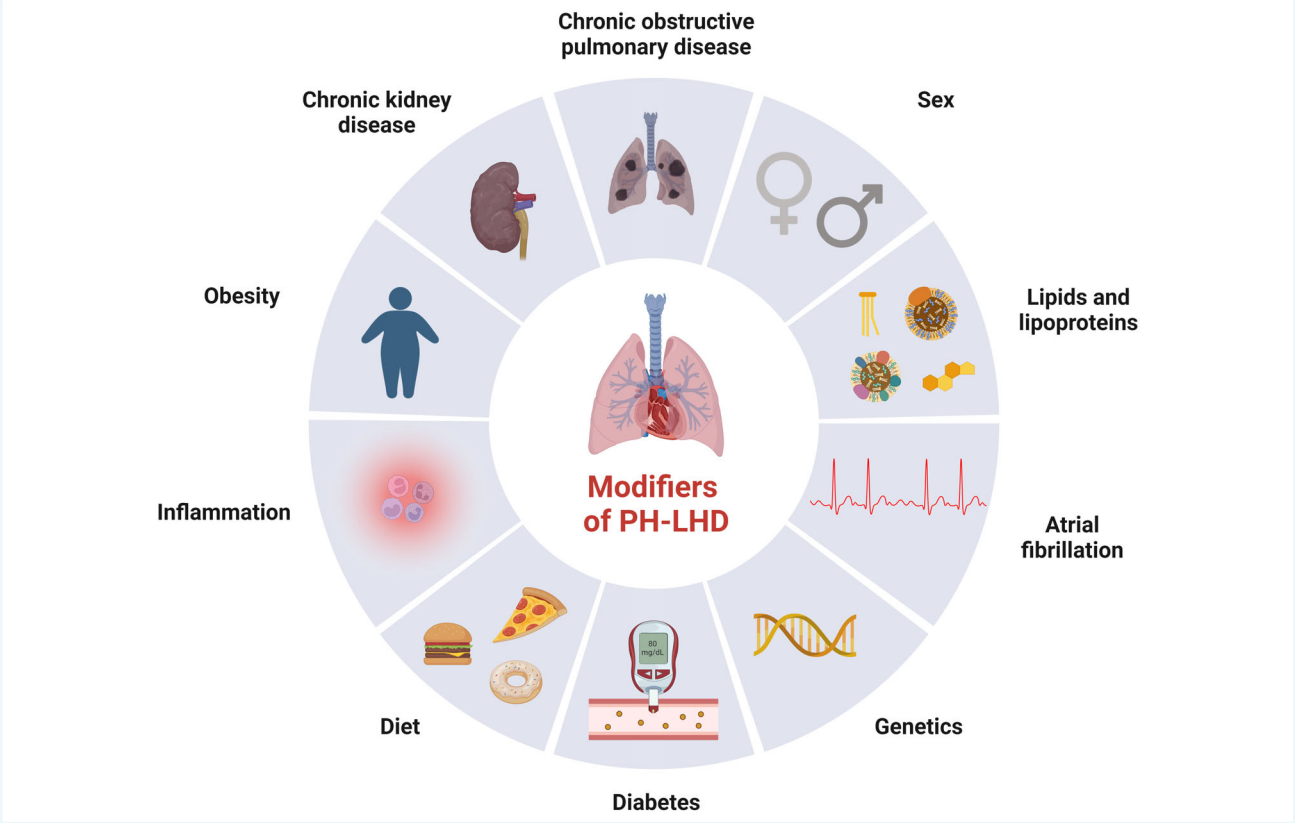

Figure 2 Comorbidities influence the pathophysiology, clinical presentation and outcomes of pulmonary hypertension associated with left heart disease (PH-LHD).

that risk of death in PH-HFpEF is higher when DL_{CO} is very low, despite the absence of overt abnormalities at chest computed tomography (CT). Nonetheless, subjects with HFpEF and markedly reduced DL_{CO} frequently have a history of smoking and might be affected by PH secondary to subclinical pulmonary disease.[78] The same question applies to patients labelled as idiopathic PAH with a history of smoking and DL_{CO} <45% of predicted, but normal or near-normal spirometry and CT, who resemble patients with group 3 PH rather than those with classical idiopathic PAH.[81] Other comorbidities do not directly cause PH, but may represent second hits on top of increased left heart pressures. Experimental evidence indicates that this occurs with metabolic syndrome.[82] Consistently, patients with PH-LHD and PVD display a greater prevalence of diabetes mellitus than those with purely post-capillary PH, even if body mass is lower.[33]

Therefore, it is crucial to recognize and treat comorbidities as they are factors favouring or even driving the development of PH in individuals with LHF.

Pulmonary function and gas exchange

Pulmonary function testing in PH-LHF allows for ruling out concomitant pulmonary pathology and may in addition provide information on pulmonary congestion and vascular remodelling.

Pulmonary congestion in decompensated LHF is reflected by reduced DL_{CO}, rather than by the forced vital capacity (FVC) or the ratio between forced expiratory volume in the first second (FEV_1) and FVC.[83] An additional drop in DL_{CO} during exercise is commonly observed in LHF due to interstitial lung water accumulation.[84] Moreover, congestion and reduced alveolo-capillary gas transfer relate to higher PVR[85] and lower PAC.[33,86]

In the absence of a pulmonary parenchymal disorder, the aforementioned disproportionate decrease of DL_{CO} in some LHF patients likely corresponds to remodelling of the arterial, capillary and also venous pulmonary vessels.[78]

Exhaled breath analysis of volatile compounds may give additional insights into PH-LHF,[87] although it has been explored in acute decompensated, instead of chronic, LHF and it remains to be demonstrated whether it can also discriminate LHF with and without PVD.

Imaging

Since RHF in response to pressure overload drives prognosis in PH-LHF, the detection of initial signs of RV-PA uncoupling may enable the identification of those patients for whom therapeutic efforts should be greatest.

Pulmonary afterload can be inferred from the velocity of the TR jet, and RV function from TAPSE[88] or three-dimensional RV ejection fraction[89]; this approach has the advantage of being universally feasible, but it is not entirely accurate. Nevertheless, the TAPSE/sPAP ratio is a marker for the presence of PH,[90] has been validated as a surrogate parameter of RV-PA coupling against conductance catheterization,[91] and serves as a prognostic indicator in PAH and PH-LHF.[25,88,92]

By contrast, echocardiography- and, particularly, cardiac magnetic resonance (CMR)-derived RV strain is less load-dependent and is an early and sensitive measure of RV-PA uncoupling and RV end-diastolic stiffness.[93,94] Importantly from the translational standpoint, RV strain can also be evaluated in animal models.[95]

Extravascular lung water can be estimated from chest radiographs,[85] by remote dielectric sensing,[96] or by lung ultrasound.[36] More precise assessment of extravascular lung water can be done by chest CT scan. As an alternative to contrast medium, artificial intelligence (AI)-based image processing can be used to separate lung parenchyma from lung vessels.[84,97] AI can enable the quantification of the pulmonary vascular tree (with pulmonary arterial pruning in exercise-induced PH[98]) or of interstitial disease developing from chronic congestion and inflammation in LHF.[83] Emerging new CT technologies such as photon counting are anticipated to enhance resolution and can be combined with automated texture analysis by AI algorithms.[99]

Haemodynamics

Right heart catheterization provides a wealth of data, which may be exploited to investigate the pathophysiology of PH-LHF and better determine the effectiveness of therapeutic interventions.

In the research setting, PAP dynamics and RV-PA coupling can be studied by analysis of the PA waveform[100,101] and pressure–volume curves obtained by simultaneous acquisition of RHC and imaging data,[102–105] respectively (*Table 2*).

The response of PAP to exercise can be also evaluated in relation to changes in CO during RHC. A slope of the relationship between mPAP and CO >3 mmHg/L/min during upright exercise is considered abnormal.[106] The increase in mPAP is caused not only by PAWP elevation, but also by PVR variations. While PVR usually decreases with exercise in healthy individuals,[107] some LHF patients, regardless of ejection fraction, develop marked increases in PVR during exercise.[26,108] This phenomenon may be secondary to exercise-induced pulmonary vasoconstriction, an early stage of PVD that is associated with a higher risk of mortality[109] and, thereby, may represent a therapeutic target.

Pulmonary artery pressure response to exercise can also be inferred by measuring PA waveforms as obtained by means of the CardioMEMS device.[110]

The combination of imaging and haemodynamic data is anticipated to further expand the possibilities of PH-LHF phenotyping by allowing exploration of RV contractile reserve.[111,112] For example, in patients implanted with the CardioMEMS sensor, use of CMR imaging has been proposed to study ventriculo–vascular coupling.[113]

Venous blood distribution

The venous system, particularly that of the splanchnic organs, serves as a large reservoir of blood.[114] Splanchnic venous tone is regulated by the sympathetic nervous system and exerts a powerful means of regulating venous pressures by creating functional shifts of blood between stressed (SBV) and unstressed (UBV) blood volume components. UBV is the volume required to fill the vasculature to the point where pressure just exceeds 0 mmHg. Blood volume above UBV is the SBV, which has also referred to the effective circulating volume since it is this component, along with vascular compliance (C), that determines vascular pressure (P): P = SBV/C. Despite being difficult to measure SBV in the clinic (and even in the experimental setting), computational methods have revealed that SBV at rest is higher in LHF (both HFrEF and HFpEF) compared to normal individuals and that SBV increases to a greater extent during exercise in patients with LHF than in normal individuals[114,115]. Increased SBV has been shown to be responsible for a large portion of the rise in central venous pressure and PAWP observed at rest and during exercise (*Figure 1*). Accordingly, venous tone may be a viable treatment target for PH-LHF.

Biomarkers and omic profiling

Targeted biomarker analyses can elucidate mechanisms and maladaptation in PH-LHF. For example, greater PH severity in HFpEF is most strongly and positively related to increases in endothelin-1, with secondary elevations in adrenomedullin, presumably as a counter-regulatory response.[116] Current advanced computational technology enables researchers to probe large scale databases relevant to circulating biomarkers, including RNAs, proteins, and lipids.[117–120] These unsupervised systems biology techniques hold great promise in unravelling the phenotypes of PH-LHF and can also reveal pathogenic disease pathways, especially when integrated with experimental investigations. Unique to PH-LHF is the possibility to collect pulmonary arterial, capillary and post-capillary blood through the wedged PA catheter during RHC. By comparing these samples with those taken in the unwedged position, transpulmonary gradients of molecules that are peculiar of PH-LHF can be detected.[121,122]

Moving towards collaborative, multi-level phenotyping

Given the complexity and multifactorial aetiology of PH-LHF, the effort at phenotyping requires a strong collaboration among various expert centres, with the goal to create large registries incorporating various parameters of interest, whether clinical, haemodynamic, imaging, tissue and biomarker biobanks, as well as various other omics data. This has been a particular mandate for the ambitious Pulmonary Vascular Disease Omics Program (PVDOMICS), which aims at leading to new understanding of PH and right heart dysfunction, based on clinical, haemodynamic, radiographic, molecular, proteomics and metabolomics characteristics.[119,123]

The need to improve pre-clinical models of pulmonary hypertension associated with left heart failure

A multitude of experimental approaches exist to mimic HF, yet there are few animal models of PH-LHF with strong translational potential. This is due to intrinsic limitations of many ways to induce HF, to the lack of screening for and poor characterization of PH-LHF, and to inter-species differences.

To make the point, an overview of the animal models developed to investigate HFpEF is presented in *Table 3* (see also references[124,125]). Rodents were used more often than larger animals, mainly pigs, and HFpEF was created by direct cardiac injury or indirectly, through the effects of hypertension, hyperlipidaemia, diabetes, obesity, and/or low-grade, chronic inflammation.

In a recent analysis,[126] all HFpEF animal models were scored based on the presence of clinical features such as preserved LV ejection fraction (LVEF), lung congestion, exercise impairment, and comorbidity burden, as well as based on the items of the two HFpEF algorithms, the HFA-PEFF score[127] and the H_2FPEF score.[128] Only three, multi-hit mouse models had a high likelihood to resemble clinical HFpEF: 15-week high-fat diet and L-NAME in C57BL6/J,[129] but not C57BL6/N[130] mice; 18–20 months aging, high-fat diet and angiotensin II infusion[131]; and 16 months of aging, high-fat diet and 3 months desoxycorticosterone pivalate.[132] Surprisingly, sex-related differences were explored only in first model, in which young female mice were more resilient to HFpEF than young male mice.[133] The bias towards assessment of only one sex is common to the majority of HFpEF animal studies. Furthermore, most of the animal investigations on HFpEF did not incorporate load-independent indices of diastolic function, such as the LV end-diastolic pressure–volume relation. Especially, as the majority of models induce systemic hypertension, load-dependent indices of diastolic function may be less reliable.[134]

The development of PH, PVD, and RV remodelling, if any, was assessed only in a minority of these animal models (*Table 3*).

It is also notable that mice only develop mild PH, and an additional stress is needed to compound PH and precipitate RV dysfunction. For instance, a single injection of the vascular endothelial growth factor inhibitor, sugen, was necessary in 8 week-old obese ZSF1-rats to attain elevated RV systolic pressures after 14 weeks.[135]

Moreover, different mouse strains display a variable degree of PH upon the same challenge: in an elegant study, only a few strains out of 36 examined proved susceptible to PH-HFpEF after 20 weeks of high-fat diet, and the 129S1/SvImJ was even resistant.[136]

Therefore, it is essential that development of new rodent models of HFpEF, as well as the refinement of the already existing ones, is systematically integrated by the study of pulmonary pressures and RV function, by analysis of lung and cardiac specimens collected at sacrifice, *in vivo* echocardiography and, ideally, RHC. Pre-clinical modelling of PH-LHF may be also improved by evaluating larger animals, which have been used far less frequently than mice and rats until now.[137]

In a recently validated piglet model, banding of the left anterior pulmonary and posterior common pulmonary veins recapitulated the haemodynamic features of post-capillary PH.[32] Interestingly, histological changes were demonstrated in pulmonary arteries and veins, confirming the relevance of venous, and not only arteriolar, remodelling in this context. Laser capture dissection of remodelled small pulmonary vessels followed by proteomics highlighted unique pathophysiologic modifications mediating venous versus arterial remodelling, with possible therapeutic implications. However, in an older study with pigs, in which post-capillary PH was obtained by non-restrictive banding of the confluent of inferior pulmonary veins, only pulmonary arteriolar remodelling was reported.[138]

Application of these methods to large animal models of HFpEF may lead to insights into the pathobiology of PH-HFpEF.

The need to improve early-phase clinical trials in pulmonary hypertension associated with left heart failure

Most of previous attempts to target PAH pathways to treat PH-LHF have been at best inconclusive, some even being associated with potential safety signals. Although many confounders may explain these disappointing results, important lessons can be learned to improve future strategy, regarding the choice of drug, study design, assessments, and patient population (*Figure 3*).

Tested drugs

Investigational compounds do not necessarily have to act only on pulmonary vessels to attenuate PH-LHF; activities in other vascular beds, as well as in the heart, may be equally important. In this respect, therapies that have been evaluated in PH-LHF include agents targeting the NO–cyclic guanosine monophosphate (cGMP) pathway, β-adrenergic agonists, and levosimendan (*Table 4*).[139–144]

Direct NO donors have many drawbacks, including induction of tolerance or increases in oxidative stress, which indeed might account for the failure of key RCTs in HFpEF.[145] Conversely, inorganic nitrite can be administered shortly before exercise to serve as a source of NO for the stressed cardiovascular system. In early clinical trials, both intravenous and inhaled sodium nitrite acutely improved exercise pulmonary haemodynamics and LV pressures and performance in individuals with HFpEF.[139,140] However, in a subsequent RCT in patients with HFpEF and rest or exercise PH, sustained therapy with nebulized nitrite for 4 weeks did not modify peak oxygen consumption, functional outcomes, the echocardiographic E/e' ratio, and NT-proBNP concentrations as compared with placebo.[146]

Levosimendan can be beneficial in PH-LHF through enhanced LV or RV contractility, but possibly also via pulmonary and systemic vasodilatation secondary to K_{ATP} channel activation in vascular smooth muscle cells and, to some extent, opening of additional K^+ channels (e.g. B_{KCa} and K_V), and endothelial NO-dependent and cAMP-related mechanisms.[147] The Hemodynamic Evaluation of

Table 3 Assessment of pulmonary hypertension in animal models of heart failure with preserved ejection fraction

	Animal type					Sex	Assessment of LV diastolic dysfunction and PH						
	Mouse	Rat	Pig	Dog	Cat		LVEF >50%	LVEDP/ EDPVR	IVRT E/A E/e'	mPAP RVSP PVR	PAAT/cl RVEDV	Pulmonary vascular remodelling	RV remodelling
Single-hit models													
Ligation left coronary artery													
Mouse[1]	✓					M + F		✓	✓	✓	✓	✓	
Rat[2,3]		✓				M		✓		✓			
Pig[4]			✓			M + F				✓			
Low-dose ANGII[5]	✓					M	✓	✓	✓				
Left atrium stenosis[6]		✓				–	✓	✓		✓		✓	
Aortic constriction													
Mouse[7,8]	✓					M		✓		✓		✓	✓
Rat[9,10]		✓				M	✓	✓	✓	✓	✓	✓	✓
Pig[11,12]			✓			M	✓	✓	✓				✓
Cat[13]					✓	M	✓	✓	✓	✓		✓	
Senescence-accelerated mouse prone 8[14]	✓					M	✓	✓	✓				
Sub-total nephrectomy[15]		✓				M	✓	✓					
ZDF[16]		✓				M	✓	✓	✓				
Dahl salt sensitive[17]		✓				M	✓	✓	✓				
db/db leptin-receptor deficient morbidly obese[18]	✓					M + F	✓	✓	✓				
High-fat high-sugar													
Mouse[19]	✓					F	✓	✓					
Pig[20]			✓			M	✓		✓				
Double hit models													
Fisher 344 + aging[21]		✓				F	✓	✓	✓				
Renal wrap + aging[22]				✓		M + F	✓	✓	✓				
High-fat diet AKR/J mice + aging[23]	✓					M	✓	✓		✓		✓	
L-NAME + high-fat diet[24,25]	✓					M + F	✓	✓	✓				
Western diet + aortic block[26,27]			✓			F	✓	✓					✓
ZSF1 obese + high-fat diet[28]		✓				M	✓	✓	✓				
DKO: leptin deficiency + LDL receptor deficiency[29,30]	✓					M + F		✓					
ZSF1 + SU5416[31]		✓				M	✓	✓	✓	✓	✓	✓	
Dahl salt sensitive + obese[32,33]		✓				M + F	✓		✓				
DOCA + unilateral nephrectomy[34]		✓				M		✓					
DOCA + western diet[35]			✓			F	✓	✓					
Multiple hit models													
DOCA + ANGII + western diet[36]			✓			F	✓	✓	✓				
High-fat diet + ANGII + aging[37]	✓					F			✓				
High-fat diet + olanzapine + supracoronary aortic banding[38]		✓				M	✓	✓	✓	✓	✓	✓	
Fisher 344 x spontaneous hypertension + aging[39]		✓				M	✓		✓				
Dahl salt sensitive + high-salt diet + aging[40]		✓				M + F	✓	✓	✓				
Hypertension + hypercholesterolaemia + diabetes mellitus[41]			✓			F	✓	✓	✓				

The relevant references are provided in online supplementary *Appendix S1*.

ANGII, angiotensin II; DOCA, deoxycorticosterone acetate; EDPVR, end-diastolic pressure–volume relation; IVRT, isovolumic relaxation time; LDL, low-density lipoprotein; L-NAME, L-NG-nitroarginine methyl ester; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PAAT/cl, pulmonary artery acceleration time normalized to cycle length; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVSP, right ventricular systolic pressure.

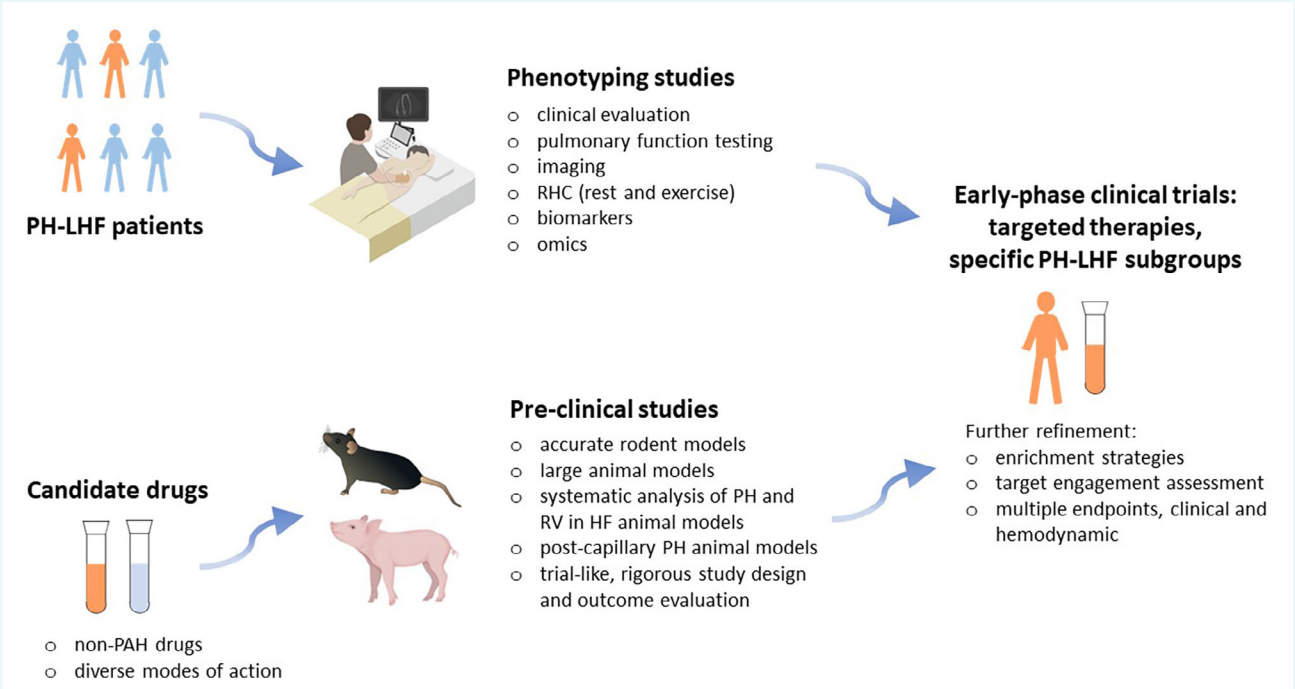

Figure 3 A roadmap for therapeutic discovery in pulmonary hypertension associated with left heart failure (PH-LHF). HF, heart failure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; RV, right ventricle.

Levosimendan in Patients With PH-HFpEF (HELP) RCT compared weekly 24-h infusions of low-dose levosimendan versus placebo in patients with HF, LVEF ≥40% and PH who had a ≥4 mmHg reduction of exercise PAWP after an initial open-label 24 h levosimendan infusion.[143] Compared with placebo, levosimendan did not significantly reduce the primary endpoint of exercise-PAWP, but did decrease PAWP and central venous pressure across all exercise stages. These results were attributed to selective venodilatation at the applied dose of levosimendan, with ensuing redistribution of blood from the central to the peripheral venous circulation, with no evidence of modulation of RV or LV contractility, PVR, or CO. Nonetheless, the numeric decrease of systemic vascular resistance just missed statistical significance and could have been contributory. 6MWD was also greater with levosimendan than with placebo. Of note, normalization of dysregulated vascular K^+ channel functions has formerly been tested in PAH using a number of drugs, but without major breakthroughs,[148] possibly because of the widespread involvement of K^+ channels in the cardiovascular system and other organ functions.[149] An open-label rollover study of levosimendan in PH-HFpEF recently showed that oral levosimendan was also safe and effective.[150]

There are β-adrenergic receptors expressed in both pulmonary endothelial and smooth muscle cells, and treatment with the inhaled β_2 agonist albuterol was reported to improve exertional PVR in PH-HFpEF, with better PA compliance, enhanced RV-PA coupling, and favourable mitigation of a steep PA pressure–flow relationship.[151] Compared with placebo, 1-week administration of the oral selective β_3 adrenoreceptor agonist mirabegron increased CI and reduced PVR at rest in a small RCT involving 22 patients with symptomatic HFrEF and elevated NT-proBNP levels.[152] Nevertheless, in the β_3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE-HF) trial, PVR did not significantly differ after 16 weeks of mirabegron versus placebo in 66 subjects with LHF and CpcPH. Of the secondary endpoints, only the modification in RV ejection fraction by CMR or CT was met (placebo-corrected mean difference of 3.0%, 95% confidence interval 0.4–5.7%).[144]

Further compounds including a long-acting relaxin mimetic are now under investigation in PH-LHF (*Table 4*).

Non-pharmacological treatments, such as breathing oxygen-enriched air, implantable PA balloon counter-pulsation,[142] and PA denervation,[141] are also noteworthy but need further appraisal.

Trial design

Phase II RCTs should be approached as the bridge from translational to clinical research and conceived as hypothesis-generating projects conducted with scientific rigour.[153]

Many are now advocating that the success of phase II RCTs should not be based on achievement of a pre-specified primary efficacy endpoint.[154] Provided no safety concerns emerge, phase II RCTs can, and often do, proceed to phase III RCTs without meeting a pre-specified primary endpoint. Indeed, phase II RCTs are expected to provide direction, not to serve as a gating event for future clinical studies. Along these lines and to gain the most possible information, it would be advantageous to decouple the achievement of statistical significance for a number of endpoints of interest, so that they are all analysed without the overriding

Table 4 Main clinical trials evaluating treatments for pulmonary hypertension associated with left heart failure other than pulmonary arterial hypertension and heart failure drugs

First author, year, acronym, NCT, reference	Study intervention	Study design/duration	No. of patients/HF type	PH definition for inclusion	Primary and secondary outcomes	Main results
Borlaug, 2015, NCT01932606[139]	Sodium nitrite 50 μg/kg/min for 5 min vs. placebo IV	Single-centre, randomized, double-blind, placebo-C/single administration	$n = 28$/LVEF ≥50%	mPAP not considered as inclusion criterion RHC data: yes	Primary: changes in PAWP during exercise Secondary: changes in resting PAWP, changes in rest and exercise right atrial pressure, PAP, PVR, systemic BP, HR, CO, VO_2 and CaO_2-CvO_2 (%)	Improvement in PAWP, increase in CO reserve, PAP-flow relationship and LV stroke work with exercise
Borlaug, 2016, NCT02262078[140]	Nebulized sodium nitrite 90 mg vs. placebo Inhaled	Single-centre, randomized, double-blind, placebo-C/single administration	$n = 26$/LVEF ≥50%	mPAP not considered as inclusion criterion RHC data: yes	Primary: changes in PAWP during exercise Secondary: changes in resting PAWP, changes in rest and exercise right atrial pressure, PAP, PAC, PVR, systemic BP, HR, CO, VO_2 and CaO_2-CvO_2 (%)	Reduction in PAWP, improvement in PAC, reduction in mPAP at rest and during exercise
Zhang, 2019, PADN-5, NCT02220335[141]	PA denervation vs. sildenafil plus sham PA denervation	Multicentre, randomized, open-label, sham-C/6 months	$n = 98$/HFpEF and HFrEF with CpcPH	mPAP ≥25 mmHg, PAWP >15 mmHg, and PVR >3 WU at RHC RHC data: yes	Primary: changes in 6MWD Secondary: changes in PVR	Improvement in 6MWD and reduction in PVR Clinical worsening less frequent in the PA denervation group than in the sildenafil group
Müller, 2021, NCT04157660[142]	Oxygen-enriched air vs. placebo Inhaled	Single-centre, randomized, single-blinded, placebo-C, crossover/single administration	$n = 10$/LVEF >50%	mPAP >25 mmHg and PAWP >15 mmHg at RHC RHC data: not available	Co-primary: changes in maximal work rate during incremental exercise test and changes in cycling time during high-intensity constant work rate exercise test	Increase in incremental exercise test and cycling time during high-intensity constant work rate exercise test
Burkhoff, 2021, HELP, NCT03541603[143]	Run-in[a] → levosimendan titrated to 0.1 μg/kg/min over 24 h weekly vs. placebo IV	Multicentre, randomized, double-blind, placebo-C/6 weeks	$n = 37$/LVEF >40%	mPAP >35 mmHg and PAWP >40 mmHg at RHC with legs elevated into the pedals of a supine cycle ergometer RHC data: yes	Primary: changes in exercise PAWP Secondary: changes during rest and exercise in CI and PVR; changes in 6MWD, WHO-FC, and composite of death and hospitalization	Reduction in PAWP measured across all exercise stages and improvement in 6MWD with levosimendan vs. placebo
García-Álvarez, 2022, SPHERE-HF[144]	Mirabegron 50 mg → 200 mg/day vs placebo Oral	Multicentre, randomized, double-blind, placebo-C/16 weeks	$n = 66$/any LVEF	mPAP ≥25 mmHg, PAWP ≥15 mmHg, and PVR ≥3 WU or TPG ≥12 mmHg at RHC RHC data: yes	Primary: changes in PVR Secondary: change in RVEF by cardiac magnetic resonance or computed tomography; changes in 6MWD, dyspnoea Borg scale, and WHO-FC; HF decompensation; death; quality of life	Primary endpoint not met Improvement in RVEF
PH-HFpEF, NCT03015402	Sodium nitrite vs. placebo Oral	Single-centre, randomized, double-blind, placebo-C, cross-over/22 weeks	$n = 26$/LVEF ≥40%	mPAP ≥25 mmHg, PAWP ≥15 mmHg and TPG ≥12 mmHg at RHC	Primary: changes in mPAP during submaximal exercise Secondary: changes in 6MWD, pulmonary haemodynamics, NT-proBNP, exercise time, and WHO-FC	Completed in 2023 (21 patients enrolled) no study results posted on ClinicalTrials.gov
PH-HFpEF, NCT03629340	Metformin vs. placebo	Single-centre, randomized, blinded, cross- over/12 weeks	$n = 10$/LVEF ≥50%	PH-HFpEF confirmed within the past 6 months (mPAP ≥25 mmHg, PAWP ≥15 mmHg and TPG ≥12 mmHg) and ≥3 features of metabolic syndrome	Primary: changes in mPAP during submaximal exercise at 12 weeks	Ongoing
Re-PHIRE, NCT05737940	Relaxin mimetic AZD3427 vs. placebo SC	Multicentre, randomized, double-blind, placebo-C/24 weeks	$n = 220$/HFpEF and HFrEF	mPAP ≥25 mmHg and PAWP ≥15 mmHg RHC data: yes	Primary: change in PVR at 24 weeks	Ongoing

6MWD, 6-min walking distance; BP, blood pressure; CaO_2-CvO_2, arterial-mixed venous oxygen content difference; CI, cardiac index; CO, cardiac output; CpcPH, combined post-capillary and pre-capillary pulmonary hypertension; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NCT, identifier number on ClinicalTrials.gov; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; placebo-C, placebo controlled; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RVEF, right ventricular ejection fraction; SC, subcutaneous; sham-C, sham controlled; TPG, transpulmonary gradient; VO_2, oxygen consumption; WHO-FC, World Health Organization functional class; WU, Wood units.

[a] Eligible patients underwent a run-in, 24-h open-label infusion of levosimendan (0.10 μg/kg/min), in order to identify those most likely to respond to a longer-term course of treatment. At the end of the 24 h infusion, rest and exercise RHC were performed and subjects with ≥4 mmHg reduction of PAWP during 3 min of exercise at 25 W, along with ≤10% decrease of CI, qualified for randomization.

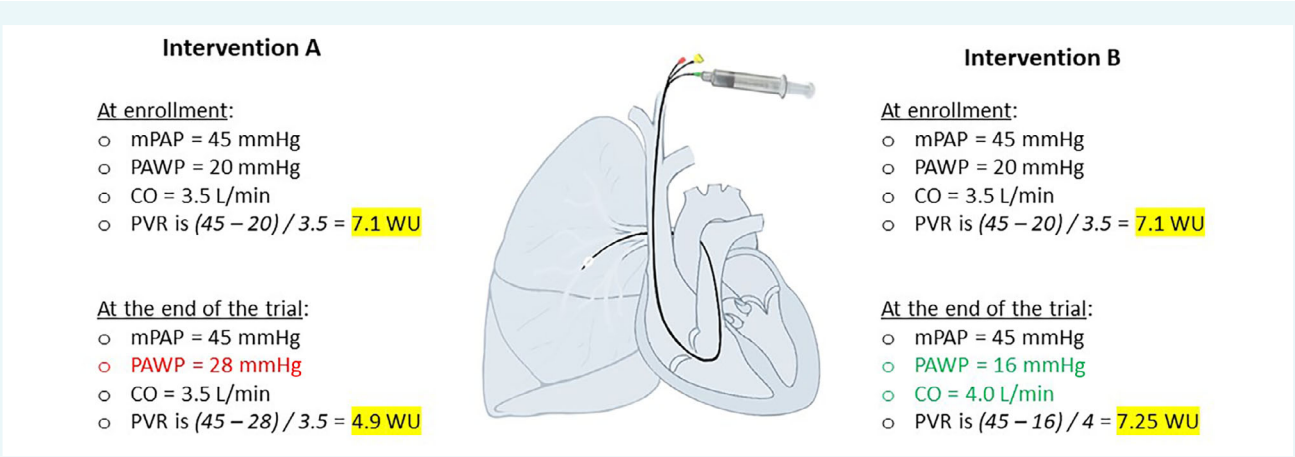

Figure 4 Potential for misinterpretation of changes in pulmonary vascular resistance (PVR) from treatments for pulmonary hypertension associated with heart failure with preserved ejection fraction (PH-HFpEF). Intervention A lowered PVR from 7.1 to 4.9 Wood units (WU) by raising pulmonary artery wedge pressure (PAWP) from 20 to 28 mmHg, a highly undesirable effect. Conversely, intervention B did not change PVR, but lowered PAWP from 20 to 16 mmHg while raising cardiac output (CO) from 3.5 to 4.0 L/min, which are very favourable effects. mPAP, mean pulmonary artery pressure.

concern of limiting the likelihood of a false-positive finding. In the end, interpretations of phase II studies are often based on impressions as much as on hard evidence.

Patient selection

Like in any field of medicine, identification of appropriate patients is of utmost importance in testing new therapies for PH-LHF. Study participants can be selected according to characteristics that make a response to the investigational treatment likely, so-called predictive enrichment.[155] This strategy can be then implemented in clinical practice, as it is the case with the acute vasodilator testing to support the use of calcium channel blockers in PAH.[156]

Alternatively, subjects with more advanced disease can be included as they have a greater likelihood of facing an adverse outcome and, thus, of benefiting from an intervention that reduces the risk of that outcome.[114] However, this strategy can backfire, in that patients who are severely ill may not benefit from any therapy.

Research into better modalities to enrich PH-HF trials for patients in whom a treatment is effective is a priority, not only for optimization of efforts but also in the prospect of precision medicine (*Figure 3*).

Endpoint selection

Pulmonary vascular resistance is a common primary endpoint in phase II RCTs in PH-LHF, but it may yield a misrepresentative result unless the individual components of that measurement, i.e. mPAP, PAWP, and CO, are analysed (*Figure 4*). Other haemodynamic variables may be preferable, but are difficult to evaluate in the context of a clinical trial. A solution is to perform a comprehensive RHC evaluation, potentially both at rest and during exercise.

It was a thorough haemodynamic characterization that allowed identification of a decrease in SBV as the mechanism underlying the reduction of PAWP and central venous pressure achieved with levosimendan in the HELP RCT.[157] Interestingly, lower SBV over a full range of exercise loads was also reported with the sodium–glucose cotransporter 2 inhibitor, empagliflozin, compared to placebo, and was correlated with the reduction in PAWP.[158] Moreover, other HF medications and splanchnic nerve blockade may be beneficial in HF via SBV modulation.[159]

The Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF-2) found no effect overall of atrial shunt relative to sham procedure in patients with HF with mildly reduced LVEF or HFpEF.[160] However, a post-hoc analysis found that subjects with elevated exercise PVR were likely to be harmed by shunt treatment, whereas those with more normal exercise PVR showed signals of benefit.[14] Notably, this difference could not be detected based upon resting PVR, but required exercise haemodynamic assessment to be discovered.

On the other hand, haemodynamic endpoints should not detract the attention from more important clinical outcomes. In DYNAMIC, riociguat improved pulmonary haemodynamics, but at the end of the study no differences were found in NT-proBNP concentrations, World Health Organization functional class, 6MWD, quality of life, and the proportion of subjects who had clinical worsening events, though this trial was not powered to assess these endpoints. Treatment-emergent adverse events were more common in the riociguat than in the placebo arm. Therefore, even if the haemodynamic endpoints were reached, it is hard to judge the RCT positive from the patient standpoint.

Involvement of patient associations

It is also advisable that RCTs are carried out at centres that can offer holistic care to patients with HF, including lifestyle indications, individually-adjusted exercise and rehabilitation programmes, and

sessions to handle anxiety and depression that may stem from living with a chronic heart condition. Patient associations should be informed about new RCTs in order to advertise the opportunity to participate and favour the exchange of experience among members. Patient associations may also usefully be involved in the design of RCTs.

Leveraging the evidence from animal models

Animal studies are commonly conducted to verify one or more hypotheses. However, they can also generate the evidence basis upon which early-phase trials are conceived.

In this context, it is essential that a stringent methodology is adopted when moving from exploratory to confirmatory pre-clinical investigations with animals, including standardized procedures for interventions and collection of data[161] (*Figure 3*). Unfortunately, this is too often not the case. Among 135 PH studies with non-human mammals published from July 2006 to June 2016 in the top five journals of the American Heart Association, only 35 reported randomization of the animals to treatment, 52 blinding of the investigators to treatment allocation, and 2 *a priori* sample size calculation or power calculation.[162]

If animal studies are accurate, the observed changes in pulmonary haemodynamics, RV function, exercise tolerance, and indices of RHF represent invaluable information to choose the endpoints for human studies.

Other metrics can be translated to clinical studies, such as blood biomarkers of drug exposure or efficacy. These can be particularly of importance when trials are neutral and questions arise about adequate dosing, and may even potentially identify super-responders. For example, a phase IIa, pilot study of a single infusion of recombinant human angiotensin-converting enzyme 2 (ACE2) has recently been performed in patients with PAH, based on prior positive evidence obtained in rodent models.[163] Before conducting the study, superoxide dismutase 2 (SOD2) and inflammatory genes were identified as markers of activation of Mas1, the receptor for the peptide produced by ACE2, in porcine pulmonary arteries; furthermore, it was confirmed that plasma SOD2 concentrations were lower in patients with PAH than in control subjects. Then, it was shown that recombinant human ACE2 ameliorated pulmonary haemodynamics in PAH patients, increased plasma concentrations of SOD2, and reduced those of markers of inflammation.[163]

In principle, this approach could be also followed by exploiting more complex omic profiles, originally described in animal models.

Conclusions

Several drugs have been evaluated for PH-LHD and PH-LHF over the last decades, with modest to no evidence of efficacy and concerns regarding safety. As a result, PH-LHF remains devoid of specific therapy yet still inflicting substantial morbidity and mortality.

The failure of the previous attempts to treat PH-LHF likely has many explanations, including insufficient attention to the multiplicity of phenotypes that actually form PH-LHF, aprioristic use of medications imported from PAH, a disconnection between animal and clinical studies, and suboptimal design of early-phase RCTs.

Awareness of the limitations of prior studies and combination of several lines of investigations coming from different fields, as highlighted in the present document, are expected to allow the discovery of disease pathways that are actionable in specific patient subsets and foster well-structured RCTs. For instance, the role of pulmonary arteriolar versus venous remodelling can be explored by integrating histological and molecular analyses in animal models and unbiased measurement of the concentrations of thousands of biomarkers in the blood enriched for factors released by the pulmonary capillary and venous endothelial cells, as obtained through the wedged Swan–Ganz catheter during RHC. Identification of pathways implicated in pulmonary venous remodelling and demonstration that this latter does underlie human PH-LHF may lay the foundations for innovative RCTs in PH-LHF.

Although PH might remain an untreatable complication of HF, the roadmap proposed here will increase the likelihood of success in therapeutic discovery for this condition.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The pictures of the heart, artery, and vein in *Figure 1* were obtained from Servier Medical ART. *Figure 2* was created with BioRender (license to Konstantinos Stellos). The pictures in *Figures 3* and *4* were obtained from Wikimedia Commons.

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