Int J Heart Fail. 2021 Jul;3(3):147-159
https://doi.org/10.36628/ijhf.2020.0053
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Review Article

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Pulmonary Hypertension in Heart Failure

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OPEN ACCESS

Received: Dec 16, 2020
Revised: Mar 19, 2021
Accepted: Mar 26, 2021

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Funding
This research was supported by grants (2018-ER6304-00 (2018), 2018-ER6304-01(2019) and 2018-ER6304-02 (2020)) from the Korea Centers for Disease Control and Prevention (Chung WJ) and Seoul R&D Program (BT190153) for research and development for regional industry (Chung WJ) and by the Korea Medical Device Development Fund grant sponsored by the Korean government

ABSTRACT

Pulmonary hypertension (PH) is traditionally defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg. Although various factors cause PH, the most common etiology is PH due to left heart disease (PH-LHD). The underlying LHD is characterized by heart failure (HF) with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), valvular heart disease, cardiomyopathies, or arrhythmic diseases. Regardless of its underlying cause, elevated left atrial (LA) filling pressure is a manifestation of advanced heart disease. High LA pressure then causes persistent backflow to the pulmonary veins, which increases mPAP. PH-LHD at this stage is named isolated postcapillary PH (IpcPH). Further progression of IpcPH is associated with pulmonary vasculature remodeling and hypertrophy, which consists of adding the precapillary component of PH to the pre-existing postcapillary PH. This form of PH-LHD is called combined precapillary and postcapillary PH (CpcPH). To date, therapeutic strategies for PH-LHD have been investigated in the context of HFrEF or HFpEF. Pulmonary arterial hypertension (PAH)-specific drugs have been tested in HFrEF and HFpEF populations, although encouraging results have not been demonstrated. As PAH-specific drugs target the precapillary component of PH-LHD, future studies utilizing such therapeutics in PH-LHD patients with CpcPH appear to have a more robust pathobiological basis. This article reviews the diagnosis, pathophysiology, treatment, and future direction of PH in HF.

Keywords: Pulmonary hypertension; Heart failure; Classification; Treatment

INTRODUCTION

Pulmonary hypertension (PH) is a condition traditionally defined as resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg.[1] PH is most commonly involved in left heart disease (LHD) with elevated left atrial (LA) filling pressure, constituting up to 65% of PH.[2-4] Recent studies have highlighted the importance of PH in LHD (PH-LHD) because the presence of PH leads to poor outcomes in patients with severe mitral regurgitation (MR),[5] transaortic valve implantation,[6] heart failure (HF) with reduced ejection fraction (HFrEF),[6] and HF with preserved ejection fraction (HFpEF).[7] Severe LHD may induce pulmonary arteriolar and venous remodeling, which subsequently promotes uncoupling between the left atrium (LA) and right ventricle (RV), leading to poor prognosis.[8] Our recent understanding of PH

(the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, Republic of Korea; and the Ministry of Food and Drug Safety) (project number: 202013B05, 202013B11) (Chung WJ).

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Jang AY, Chung WJ; Data curation: Jang AY; Formal analysis: Jang AY; Visualization: Jang AY; Writing - original draft: Jang AY, Park SJ; Writing - review & editing: Jang AY, Chung WJ.

in HF has significantly advanced through a worldwide effort.[8] In this review, we discuss the classification, pathophysiology, and relevant therapeutic strategies of PH in HF.

HOW IS PH-LHD CLASSIFIED?

Classification of PH by the World Symposium

In 1973, PH was initially classified into 2 categories: primary PH and secondary PH. In 1988, the current 5 categories were proposed at the Second World Symposium on PH (WSPH) held in Evian, France[9] comprising the current 5 group categories announced by the World Health Organization.[1] Group I PH is pulmonary arterial hypertension (PAH). Group II PH is PH-LHD. Group III is PH caused by concurrent lung disease and hypoxia by other pulmonary artery obstructions. Group IV PH consists mainly of chronic thromboembolic PH. Group V is defined as PH caused by a complex or unknown etiology.

Definition and the diagnosis of PH-LHD: isolated postcapillary PH (IpcPH) and combined precapillary and postcapillary PH (CpcPH)

PH can also be defined hemodynamically as a phenotype based on mean pulmonary pressure (mPAP), diastolic pressure gradient (DPG), and pulmonary vascular resistance (PVR) measured by invasive right heart catheterization (RHC).[10] Precapillary PH refers to PH caused by pulmonary artery and arteriolar remodeling, whereas postcapillary PH is equivalent to PH-LHD. Thus, postcapillary PH involves elevated left ventricular end-diastolic pressure (LVEDP), left atrial pressure (LAP), or pulmonary artery wedge pressure (PAWP), unlike precapillary PH. Elevated mPAP was defined as mPAP ≥25 mmHg at rest by the 2015 European guidelines.[11] Postcapillary PH was subsequently categorized into a newly introduced concept at the 5th WSPH: IpcPH and CpcPH. IpcPH was defined as PH-LHD (mPAP ≥25 mmHg and PAWP >15 mmHg) with DPG <7 mmHg and/or PVR ≤3 WU, whereas CpcPH was defined as PH-LHD combined with PVR >3 and/or DPG ≥7 mmHg (**Table 1** and **Figure 1**).[10-12] DPG is the pressure difference between diastolic pulmonary arterial pressure and mean PAWP. IpcPH is PH caused by backward transmission of high LAP or LVEDP regardless of the underlying presence of valvular disease, HFrEF, or HFpEF (**Figure 1**).[13-15] Over time, this further triggers vasoconstriction and structural remodeling of the precapillary component of pulmonary vessels. Histologically, intimal and medial hypertrophy in pulmonary arteries is observed, and it results in pathologic obstruction of distal pulmonary arteries and subsequent dramatic elevation of PVR.[14][16] CpcPH is thus understood in the context of advanced IpcPH. CpcPH is rarer than IcpPH and associated with poorer outcomes compared with IpcPH.[13][17] The

Table 1. The hemodynamic definition of pulmonary hypertension due to left heart disease

Characteristics	mPAP	PAWP	PVR	DPG
5th WSPH				
PH-LHD			N/A	N/A
IpcPH	≥25 mmHg	>15 mmHg	≤3 WU	<7 mmHg
CpcPH			>3 WU	≥7 mmHg
6th WSPH				
PH-LHD			N/A	N/A
IpcPH	≥20 mmHg	>15 mmHg	≤3 WU	N/A
CpcPH			>3 WU	N/A

mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; DPG = diastolic pressure gradient; PH-LHD = pulmonary hypertension due to left heart disease; N/A = not available; WU = wood unit; IpcPH = isolate postcapillary pulmonary hypertension; CpcPH = combined precapillary and postcapillary pulmonary hypertension.

https://doi.org/10.36628/ijhf.2020.0053

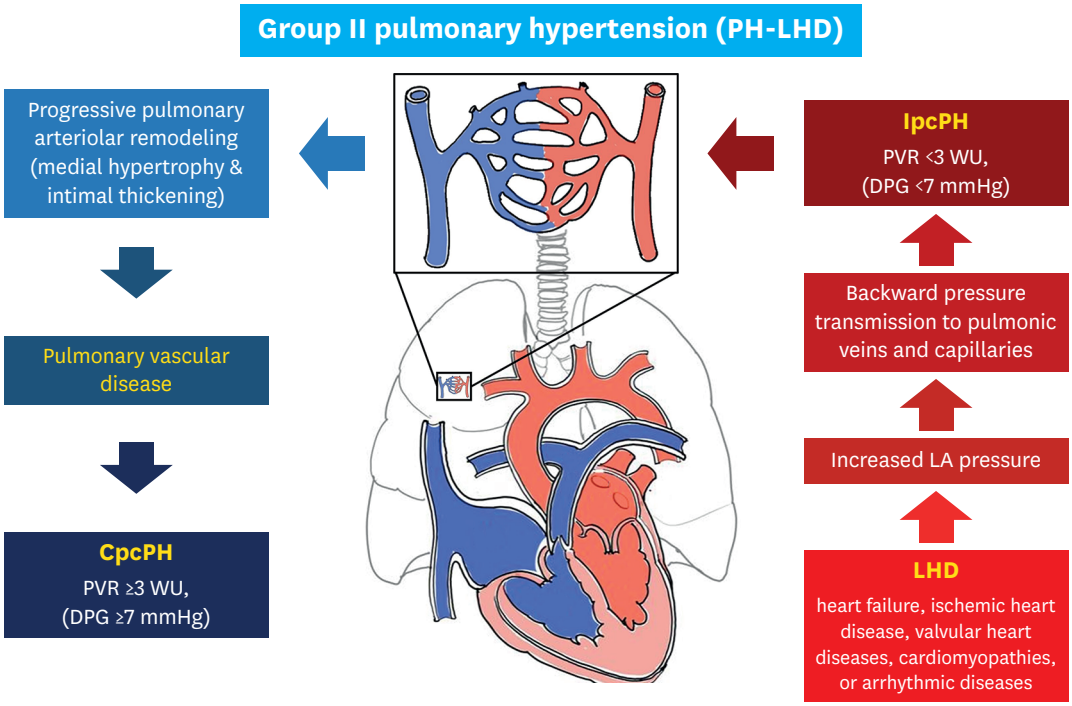

Figure 1. A schematic of the underlying mechanism of LHD transitioning to CpcPH through IpcPH. This figure shows LHD leading to increased LA pressure, which further triggers continuous back pressure transmission to the pulmonary vasculature. PH at this stage is defined as IpcPH. As the underlying LHD disease advances, progressive pulmonary arteriolar remodeling occurs, further elevating PVR. This is called CpcPH. An illustration of the precapillary and postcapillary network of the pulmonary vasculature. The definitions of IpcPH and CpcPH are shown. At the 5th WSPH, IpcPH was defined as PH-LHD (mPAP ≥25 mmHg and PAWP >15 mmHg) with DPG <7 mmHg and/or PVR ≤3 WU, whereas CpcPH was defined as PH-LHD combined with PVR >3 and/or DPG ≥7 mmHg. The subsequent 6th WSPH made modifications to the definition of PH-LHD and mPAP.[22] However, in the 6th WSPH, DPG was removed from the criteria distinguishing IpcPH and IpcPH, leaving PVR as the only criterion.
DPG=Diastolic PAP–Mean PAWP; LHD = left heart disease; CpcPH = combined precapillary and postcapillary pulmonary hypertension; IpcPH = isolated postcapillary pulmonary hypertension; LA = left atrial; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WSPH = World Symposium on pulmonary hypertension; PH-LHD = pulmonary hypertension due to left heart disease; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; DPG = diastolic pressure gradient; WU = wood unit.

problem with the definition IpcPH and CpcPH in the 5th WSPH was that patients with isolated PVR >3 or DPG ≥7 mmHg could potentially be classified into both IpcPH or CpcPH.[18] Additionally, DPG was demonstrated to have a poor predictive performance for outcomes compared with PVR.[18-21]

The 6th WSPH made modifications to the definition of LHD-PH and mPAP.[22] First, DPG was removed from the criteria distinguishing IpcPH and IpcPH, leaving PVR as the only criterion.[1] PH-LHD combined with or without elevated PVR (PVR ≥3) was defined as CpcPH or IpcPH, respectively (**Table 1**). [12][23][24] Additionally, the cutoff value of mPAP ≥25 mmHg was lowered to mPAP ≥20 mmHg in PH-LHD, as many studies have proven poor outcomes in those with mPAP between 20 mmHg and 25 mmHg.[24][25]

CORRECTING LHD IMPROVES PH-LHD

There exists evidence that correcting the underlying LHD improves PH-LHD. Correcting the underlying LHD by left ventricular assist devices (LVADs), MR clipping devices, or wireless volume status monitoring devices has shown promising results.

https://doi.org/10.36628/ijhf.2020.0053

The implantation of LVADs in PH-LHD patients who are heart transplantation (HTPL) candidates has consistently been shown to reduce PAWP, mPAP, and PVR. Among advanced LHD patients with PH-LHD, the presence of CpcPH is a contraindication for HTPL due to the high risk of postoperative adverse outcomes.[4] LVAD has consistently been shown to improve PH profiles in patients with or without CpcPH by unloading and reducing LV filling pressures (**Table 2**).[26-27] Accordingly, LVAD has become a useful option in CpcPH patients as a bridging therapy for HTPL or, in some cases, a final destination.

MR is one of the most common valvular diseases worldwide. Recently, a novel minimally invasive procedure called MitraClip therapy was introduced. The MitraClip device clips the mitral valve to repair MR, and it shows promising outcomes with low periprocedural complication rates.[28][29] The beneficial effects of the MitraClip are not only demonstrated on the left heart but also well documented to improve PH-LHD-related hemodynamics (**Table 2**).[30] In a retrospective study, the MitraClip procedure was associated with reduced tricuspid regurgitation, pulmonary artery systolic pressure, and increased tricuspid annular plane systolic excursion in patients with severe MR.[30]

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association (NYHA) Class III Heart Failure Patients (CHAMPION) trial recruited a total of 550 patients with NYHA class III symptoms, irrespective of left ventricular ejection fraction (LVEF) (**Table 2**).[31] A wireless pulmonary artery monitoring device was implanted in the pulmonary artery. Daily pulmonary artery pressure was sent to the responsible physician for assessment of optimal medical therapy. The results showed that diuretic titration based

Table 2. Studies showing that correcting left heart disease improves pulmonary hypertension due to left heart disease

Device/procedure type	Duration	Sample size	Inclusion	Endpoint	Hemodynamic results	Clinical symptoms	Hard endpoints
LVAD							
Continuous vs. pulsatile LVAD device[25]	6 weeks	35	HTPL candidates with PH	PVR	PVR was significantly reduced regardless of continuous or pulsatile LVAD device	N/A	N/A
LVAD device[26]	6 months, 6–12 months, and >12 months	145	HTPL candidates with CpcPH and IpcPH	mPAP, PVR, and TPG	mPAP, PVR, and TPG was decreased significantly	N/A	N/A
Continuous flow LVAD vs. medical therapy[27]	5 months	10 for LVAD, 14 for medical therapy	HTPL candidates with CpcPH	TPG, PVR, and all-cause mortality	TPG and PVR was improved with continuous flow LVAD	N/A	No difference in mortality
MitraClip							
MitraClip[28]	12 months	78	Symptomatic severe MR	NYHA class, MR grade, LVESV, LVEDV, and 12-month mortality	Decreased MR grade, LVEDV, and LVESV, suggestive of LV reverse remodeling	Improvement in NYHA class	No difference in matched mortality-(decreased hospitalization rate)
MitraClip vs. medical therapy[29]	24 months	614 (312 for each group)	Symptomatic severe MR	HF hospitalization and all-cause mortality	N/A	N/A	Reduction in hospitalization and all-cause mortality
MitraClip[30]	12 months	70	Severe MR with PH-LHD	TR, sPAP, and TAPSE	Improvement in TR, sPAP, and TAPSE	N/A	N/A
CardioMEMS							
CardioMEMS[31]	15 months	550	NYHA III irrespective of LVEF	HF hospital	37% reduction of HF hospitalizations at 15 months	N/A	N/A

LVAD = left ventricular assist device; PVR = pulmonary vascular resistance; PH = pulmonary hypertension; IpcPH = isolated postcapillary pulmonary hypertension; mPAP = mean pulmonary artery pressure; TPG = transpulmonary gradient; CpcPH = combined precapillary and postcapillary pulmonary hypertension; NYHA = New York Heart Association; MR = mitral regurgitation; PH-LHD = pulmonary hypertension due to left heart disease; LV = left ventricular; TR = tricuspid regurgitation; LVEF = left ventricular ejection fraction, LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; HF, heart failure; N/A = not available; HTPL = heart transplantation.

https://doi.org/10.36628/ijhf.2020.0053

on the device reduced HF hospitalization by 37% (95% confidence interval, 0.52–0.77; p<0.001) at 15 months. Together, these therapies show that correcting the underlying LHD translates to better outcomes through improved PH-LHD.

PAH-SPECIFIC THERAPY IN PH-LHD

PAH-specific drugs have been tested in PH-LHD by many studies. PAH-targeting drugs include phosphodiesterase 5 inhibitors (PDE5i), prostacyclin analogs, guanylyl cyclases, and endothelin receptor antagonists (ERAs). Most trials have been conducted in either HFrEF or HFpEF patients (**Table 3**).

Table 3. A summary of trials investigating treatment strategies of pulmonary hypertension in heart failure

Medication/device	Dose	Duration	Sample size	Inclusion	Primary endpoint	Results
PDE5i						
Sildenafil[32]	50 mg tid	24 weeks	44	HFpEF (LVEF ≥50%)	Pulmonary hemodynamics and RV performance in 1-year	Significant improvements in mPAP and RV function
Sildenafil (RELAX trial)[33]	20 mg tid	12 weeks	216	HFpEF (LVEF ≥50%)	Change in peak oxygen consumption after 24 weeks	No significant improvement
Sildenafil[34]	60 mg tid	12 weeks	52	HFpEF (LVEF ≥45%)	Change in mPAP after 12 weeks	No significant improvement
Sildenafil (SIOVAC trial)[35]	40 mg tid	6 months	200	Persistent PH after surgical correction of VHD	Composite clinical score	Worsening in clinical outcomes
Sildenafil[36]	100 mg daily	68±58 days	6	HTPL candidates with CpcPH	PVR	Sildenafil lowers PVR in HTPL candidates with CpcPH
Sildenafil[37]	75 mg tid	12 to 15 weeks	58 (26 in sildenafil + LVAD; 32 in LVAD control)	Post-LVAD patients with persistent CpcPH	12 to 15 weeks change in PVR and dP/dtmax/IP	Significant decrease in PVR
Sildenafil[38]	140 mg/day	163 days	119	CpcPH patients with scheduled HTPL	mPAP, PVR, and TPG	Improved pulmonary hemodynamics with sildenafil + HTPL compared with HTPL without sildenafil
Prostacyclin analog						
Epoprostenol[39]	Rapid uptitration until a dose of 16 ng/kg/min	12 weeks	33	NYHA III–IV, HFrEF (LVEF ≤30%)	HF signs and symptoms and 6-minute walk test	A significant decline in both PVR and mPAP and increase in cardiac index
Epoprostenol (FIRST Trial)[40]	2 ng/kg/min until dose-limiting adverse	Early termination	471	NYHA IIIB-IV, HFrEF (LVEF <25%)	Survival	A strong trend toward decreased survival
Guanylyl cyclase						
Riociguat (LEPHT)[41]	placebo, 0.5 mg tid, 1 mg tid, 2 mg tid=2:1:1:2	16 weeks	201	HFrEF (LVEF ≤40%) mPAP ≥25 mmHg at rest	Change in mPAP from baseline to week 16	Improved cardiac index and PVR
Riociguat (DILATE-1 trial)[42]	0.5, 1 or 2 mg tid	Within 6 hours after a single dose	48	HFpEF (LVEF >50%) PH (mPAP ≥25 mmHg PAWP ≥15 mmHg at rest): mostly IpcPH	Peak change from baseline within 6 hours after a single dose of study drug	No significant improvement
Riociguat (DYNAMIC trial) (NCT02744339)	0.5 mg tid uptitrated to maximum 1.5 mg tid	26 weeks	114	HFpEF (LVEF >50%) PH (mPAP ≥25 mmHg PAWP ≥15 mmHg)	Change from baseline to 26 weeks of cardiac output at rest	Study is ongoing
Vericiguat (SOCRATES REDUCED)[43]	High dose (1.25 mg qd, 2.5 mg qd, 5 mg qd, 10 mg qd: placebo)	12 weeks	456	HFrEF (LVEF <45%)	Change in NT-proBNP level at 12 weeks	No significant effect on change in NT-proBNP level at 12 weeks
Vericiguat (SOCRATE SPRESERVED)[44]	1.25 or 2.5 mg fixed doses/5 or 10 mg titrated from a 2.5 mg starting dose, qd	12 weeks	477	HFpEF (LVEF >45%)	Change in log-transformed NT-proBNP and left atrial volume	No significant improvement

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Table 3. (Continued) A summary of trials investigating treatment strategies of pulmonary hypertension in heart failure

Medication/device	Dose	Duration	Sample size	Inclusion	Primary endpoint	Results
ERA						
Bosentan (REACH-1)[45]	500 mg bid (bosentan slow/rapid titration/ placebo)	26 weeks	370	HFrEF NYHA IIIB-IV	Change in clinical status after 26 weeks of therapy	Increased HF in first month/decreased HF in 4th month
Bosentan (ENABLE)[46]	62.5 mg bid	9 months	1,613	HFrEF NYHA IIIB-IV	Clinical status at 9 months	No improvement of clinical course with increased risk of peripheral edema
Macitentan (MELODY-1)[47]	10 mg qd	12 weeks	63	CpcPH	Assessed a composite of significant fluid retention or worsening	Significant fluid retention or worsening functional class and no change in NT-proBNP

PDE5i = phosphodiesterase 5 inhibitor; LVAD = left ventricular asist device; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; RV = right ventricular; HFrEF = heart failure with reduced ejection fraction; VHD = valvular heart disease; NYHA = New York Heart Association; HF = heart failure; PVR = pulmonary vascular resistance; ; IpcPH = isolated postcapillary pulmonary hypertension; NT-proBNP = N-terminal probrain natriuretic peptide; CpcPH = combined precapillary and postcapillary pulmonary hypertension; PH = pulmonary hypertension; HTPL = heart transplantation; TPG = transpulmonary gradient; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; SIOVAC = Sildenafil for Improving Outcomes after Valvular Correction; FIRST = Flolan International Randomized Survival Trial; LEPHT = Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial; DILATE-1 = Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure; DYNAMIC = Pharmacodynamic Effects of Riociguat in Pulmonary Hypertension and Heart Failure with Preserved Ejection Fraction; SOCRATES REDUCED = Soluble guanylate Cyclase stimulator in Heart failure; SOCRATE SPRESERVED = Soluble Guanylate Cyclase Stimulator in Heart Failure Patients with Preserved Ejection Fraction; REACH-1 = Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease; ENABLE = Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; MELODY-1 = Macitentan in Subjects with Combined Pre- and Post-capillary Pulmonary Hypertension due to Left Ventricular Dysfunction.

PDE5i IN PH-LHD

PAH-specific therapies were first expected to improve HF. Many trials have tested the effect of PDE5is, which are one of the most widely used PAH-targeting drugs, although the results are conflicting (**Table 3**). In a single-center small-sample study (n=44), sildenafil was associated with improved mPAP and RV function in patients with HFrEF.[32] However, these results were not replicated in subsequent studies with larger sample sizes.[33][34] Interestingly, in patients with persistent PH even one year after valvular surgery, the use of sildenafil was associated with worsening clinical outcomes compared with the placebo.[35]

The effect of sildenafil was also investigated in candidates for HTPL (**Table 3**). LVAD implantation has gained popularity, as it has shown promising results in improving PVR in those contraindicated for HTPL due to CpcPH (**Table 2**). However, there are certain patients whose PVR does not decrease even after LVAD therapy. The effect of sildenafil was tested in a pilot study (n=6) showing that sildenafil successfully lowered PVR in HTPL candidates with CpcPH (**Table 3**).[36] In another study, 26 patients with LVAD and sildenafil therapy were compared with LVAD therapy alone (**Table 3**).[37] The sildenafil treatment group was associated with improved PVR. Sildenafil was also studied in CpcPH patients with scheduled HTPL. When sildenafil was administered, the post-HTPL pulmonary hemodynamics were improved compared with those in the patients who were not given sildenafil (**Table 3**).[38] These data indicate that sildenafil therapy may make HTPL possible in CpcPH patients contraindicated for surgery and even translate to better long-term HTPL outcomes.

PROSTACYCLIN ANALOGS IN PH-LHD

Few data are currently available regarding prostacyclin analogs in PH-LHD. Sueta and colleagues showed that intravenous (IV) epoprostenol administration significantly reduced

PVR and mPAP while increasing the cardiac index in HFrEF patients (**Table 3**).[39] However, the following Flolan International Randomized Survival Trial (FIRST) study showed conflicting data. A total of 471 HFrEF patients were recruited in the FIRST trial. The study was terminated early due to the substantial trend of increased mortality in the IV epoprostenol group.[40]

GUANYLYL CYCLASES IN PH-LHD

Most studies investigating the effect of guanylyl cyclases in PH-LHD did not show a proven benefit. In the Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) study, the riociguat group showed no difference in mPAP compared with the placebo in patients with PH-HFpEF, although there was an improvement in PVR, cardiac index, and the stroke volume index (**Table 3**).[41] The Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure (DILATE-1) study also demonstrated that riociguat treatment did not improve mPAP.[42] Another trial investigating riociguat, the Pharmacodynamic Effects of Riociguat in Pulmonary Hypertension and Heart Failure with Preserved Ejection Fraction (DYNAMIC) trial (NCT02744339) is currently underway to validate the effects of riociguat on the improvement of cardiac output in PH-HFpEF patients. Vericiguat was also investigated in both HFrEF[43] and HFpEF patients,[44] but the results showed that vericiguat was not associated with benefit in terms of natriuretic peptide levels or LA volume compared with the placebo group (**Table 3**).

ERAs IN PH-LHD

Clinical trials using ERAs in PH-LHD patients did not show a benefit, but a trend of more peripheral edema was observed (**Table 3**). Early studies using bosentan showed that when bosentan was administered and rapidly titrated to 500 mg twice daily in HFrEF patients, there was a higher probability of HF-related hospitalizations in the first month, whereas the probability of HF-associated admissions was reduced at the fourth month (**Table 3**).[45] The bosentan-treated group was also associated with higher liver enzyme levels as well as decreased hemoglobin.[45] The Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) trial enrolled HFrEF patients and evaluated the change in clinical status at 9 months of treatment (**Table 3**).[46] However, the bosentan treatment arm did not exhibit improved clinical course or natural history of the disease. Bosentan was also associated with an increased risk of fluid retention and peripheral edema.[46] The ENABLE trial was a large-scale (n=1,613) randomized control trial that compared bosentan and a placebo in HFrEF patients. The results were discouraging because bosentan was associated with significantly more peripheral edema, while outcomes were not improved.[46] The Macitentan in Subjects with Combined Pre- and Post-capillary Pulmonary Hypertension due to Left Ventricular Dysfunction (MELODY-1) trial investigated the efficacy of macitentan in RHC-confirmed CpcPH patients. Macitentan also did not show a clinical benefit, while peripheral edema and fluid retention were observed.[47] The reason behind worsening HF and fluid retention associated with ERA is not fully understood. However, it is thought to be accounted for by the negative inotropic effect of ERA[48] and interference with normal pulmonary vasoconstriction, which prevents transudation of blood flow into the alveoli when pulmonary venous pressure is increased (**Table 3**).[49]

https://doi.org/10.36628/ijhf.2020.0053

NOVEL THERAPIES AND DEVICES IN PH-LHD

Previous studies have shown the effect of inhaled or infused sodium nitrite in subjects with HFpEF (**Table 4**).[50][51] Inhaled sodium nitrite was shown to reduce PVR in patients with severe PH-LHD compared with controls. Infusion of sodium nitrite during invasive cardiac catheterization also significantly lowered PAWP and mPAP levels (**Table 4**).[51] One of the crucial pathways of PH is the nitric oxide (NO) pathway. NO secretion is possibly impaired during exercise. However, when exogenous sodium nitrite is administered to the body, it has a longer half-life than NO, leading to prolonged vasodilatory effects in the pulmonary vasculature; thus, that sodium nitrite may be a good therapeutic candidate for PH-LHD.

Levosimendan is a calcium-sensitizing agent that binds to troponin C and increases cardiac contractility without elevating cAMP levels. Levosimendan treatment in HFrEF subjects was shown to dose-dependently improve symptoms and hemodynamics (lower PAWP, mPAP, and PVR and increased cardiac contractility) without apparent adverse events.[52] The currently ongoing Hemodynamic Evaluation of Levosimendan in PH-HFpEF (HELP) phase 2 trial (NCT03541603) is likely to validate the efficacy of levosimendan in patients with PH-LHD, particularly those with HFpEF (**Table 4**).

Pulmonary artery denervation (PADN) may also be a promising option for PH. A recent study showed that PADN using the TIVUS™ ultrasound system significantly reduced PVR and increased the 6-minute walking distance in subjects with chronic thromboembolic PH (**Table 4**).[53]

Table 4. Other therapies of pulmonary hypertension in heart failure

Medication/device	Dose	Duration	Sample size	Inclusion	Primary endpoint	Results
Sodium nitrite						
Sodium nitrite[50]	Inhaled sodium nitrite	Immediate	14	HFpEF with PH (mPAP ≥25 mmHg, PAWP >15 mmHg, and TPG >12 mmHg)	PVR, RV efficiency	Reduced PVR and improved RV efficiency
Sodium nitrite (NCT01932606)[51]	50 mcg/kg/min	Infusion for 5 minutes during the cardiac catheterization procedure	28	HFpEF (LVEF >50%) resting PAWP >15 mmHg and/or PAWP ≥25 mmHg during exercise	Exercise PAWP during repeat exercise run, approximately 30 minutes after study drug administration	Sodium nitrite lowered exercise-induced PAWP and mPAP
Calcium sensitizer						
Levosimendan[52]	Uptitrated over 4 hours	6 hours	46	HFrEF ≤30% and PAWP >15 mmHg (NYHA III or IV)	PAWP, mPAP, and PVR	Reduction of PAWP, mPAP, and PVR in the treatment group
Levosimendan (HELP trial NCT03541603) ongoing	2.5 mg/mL injectable solution (0.075–0.1 μg/kg/min for 24 hours [weekly])	6 weeks	38	HFpEF (LVEF ≥40%) NYHA class IIB–III group 2 PH (PAP ≥35 mmHg, PAWP ≥20 mmHg)	Change from baseline PAWP with bicycle exercise	Ongoing
Pulmonary denervation						
Pulmonary denervation (TROPHY-II trial) (NCT03611270)[53]	TIVUS™ System	12 months	PADN group; 25/MED group; 2,515	Either HFpEF or HFrEF NYHA II–III group 2 PH, CpcPH	Safety and initial effectiveness of the TIVUS™ System when used for pulmonary artery denervation	Improvement in mPAP, PVR, TAPSE and RV FAC

TAPSE = tricuspid annular plane systolic excursion; RV FAC = right ventricular fractional area change; HFpEF = heart failure with preserved ejection fraction; PH = pulmonary hypertension; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; TPG = transpulmonary gradient; PVR = pulmonary vascular resistance; RV = right ventricle; LVEF = left ventricular ejection fraction; PAP = pulmonary arterial pressure; PADN = pulmonary artery denervation; MED = medical therapy ; HFrEF = heart failure with reduced ejection fraction; CpcPH = combined precapillary and postcapillary pulmonary hypertension; NYHA = New York Heart Association; HELP = Hepatic Encephalopathy: Lactulose vs. Polyethylene Glycol 3350-Electrolyte Solution; TROPHY-II = Treatment of Pulmonary Hypertension Group II Study.

https://doi.org/10.36628/ijhf.2020.0053

PERSPECTIVES

The reasons behind the disheartening results of most trials investigating PAH-specific therapy in PH-LHD are poorly understood. However, several suggestions could be made. The heterogeneous patient population may account for failing trial results. Most trials using PAH-specific therapies enrolled either HFpEF or HFrEF patients (**Table 3**). Most PAH-specific drugs are vasodilators and are approved for PAH, which is PH predominantly owing to the precapillary component. Among all PH-LHD populations, only 5% of patients have CpcPH, which has the precapillary component.[13)17)] Recent studies have shown that CpcPH has a stronger hemodynamic phenotypic resemblance to PAH than its IpcPH counterpart.[54)55)] PAH-specific therapies designed to target the precapillary component in the majority of PH-LHD patients without the precapillary component (IpcPH) may be a pitfall of the initial hypothesis in such studies. Among many trials, the MELODY-1 trial is the first and only study to test the effect of a PAH-specific drug in hemodynamically well-defined CpcPH patients confirmed by RHC.[47)] Unfortunately, the results showed that the use of macitentan increased fluid retention and did not translate to improved PVR (**Table 3**). The results are unexpected considering the strong photobiologic rationale of ERA specifically targeting the precapillary component of CpcPH.

Currently, there is no clear consensus treatment of CpcPH patients due to prosthesis-patient mismatch (PPM) or end-stage HF patients with CpcPH who do not respond to LVAD. PPM is a condition caused when the prosthetic valve's effective orifice area is too small for the patient body size. Previous studies show that secondary PH occurs in PPM caused by the mitral valve and is associated with poor outcomes.[56-58)] PDE5i vasodilators may be a legitimate option to alleviate vasoconstriction and possibly reverse remodeling of the pulmonary vasculature. As we encounter some mitral PPM patients who do not respond to vasodilators, stratifying patients who do or do not respond to medical therapy may also be an exciting topic for further investigation. On the other hand, a certain proportion of CpcPH patients do not improve with LVAD implantation. A recent study tested sildenafil for its effect in such patients and reported encouraging results.[27)] Identifying subgroups within CpcPH who benefit from medical therapy may also be intriguing.

With recently approved or soon-to-be-approved PAH-specific therapies, such as ERAs, guanylyl cyclases, and IV prostacyclin analogs, the treatment of PH has gained interest in Korea.[59-63)] For a more personalized approach to PAH treatment, our group has recently demonstrated the prevalence and hemodynamic characteristics of bone morphogenic protein receptor type 2 in Korean PAH subjects.[64)] Additionally, as an effort to have a comprehensive understanding of Korean PH patients through deep phenotyping, our group further launched a nationwide platform for gathering clinical phenotypes and biological samples in PH patients in Korea.[65)] This platform has currently initiated recruitment of group I PH (PAH) patients, and it will extend its investigations to group II PH (PH-LHD) in 2021 and to all other groups in the following years. Deep phenotyping analyses of the whole genome and proteomics are currently underway to provide us with a better understanding of PH patients. These efforts may open new gates for personalized medicine in PH-LHD.

CONCLUSION

Previous trials evaluating the efficacy of PAH-specific drugs in PH-LHD have been conducted in HFrEF or HFpEF patients. PAH-specific drugs exert their action on the precapillary

https://doi.org/10.36628/ijhf.2020.0053

component. Accordingly, the PAH-specific drugs in either HFrEF or HFpEF, which are not defined based on the presence of precapillary PH, may not translate to meaningful results. Patients with precapillary pathology, such as CpcPH, may be a promising population for PAH-specific drugs in PH-LHD.

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