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Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction

Victor M. Moles

Gillian Grafton

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Victor M. Moles, MD[a,*], Gillian Grafton, DO[b]

KEYWORDS

• Heart failure with preserved ejection fraction • Pulmonary arterial hypertension
• pulmonary hypertension

KEY POINTS

- Pulmonary hypertension can be frquently associated with HFpEF and is associated with worsened symptoms and mortality.
- Although right heart catheterization is the gold standard for diagnosing pulmonary hypertension, the echocardiogram raimains the screening test of choice and provides insightful information about hemodynamics.
- Currently, therer are no pulmonary hypertension sppecific medications approaved for PH-HFpEF and treatment remains focused to optimizing co-morbidities.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a common entity that predominately affects older adults. Epidemiologic trends show that the incidence of HFpEF has not declined as profoundly as heart failure with reduced ejection fraction (HFrEF), and overall mortality remains unchanged.[1] Pulmonary hypertension (PH) is a heterogeneous condition defined hemodynamically as an elevation of pulmonary artery (PA) pressures and is commonly associated with HFpEF. Clinically, PH can be classified into 5 distinct categories based on the etiology, underlying pathophysiology, and potential treatment options.[2] Of these categories, PH due to left heart disease (PH-LHD) is frequently seen in clinical practice and is most commonly a consequence of the underlying left heart condition and probably related to its severity and duration.[3,4] The association of PH and HFpEF (PH-HFpEF) can be found in a majority of patients with HFpEF and is associated with worse symptoms and increased mortality.[5]

Despite the advancements in the treatment of other forms of PH, such as pulmonary arterial hypertension (PAH), pulmonary hypertension due to interstitial lung disease (PH-ILD) and chronic thromboembolic pulmonary hypertension (CTEPH), effective treatment of PH-LHD has not been found yet.[6–9]

HOW SHOULD PULMONARY HYPERTENSION-HEART FAILURE WITH PRESERVED EJECTION FRACTION BE DEFINED?

PH was traditionally defined as a mean PA pressure $\geq$ 25 mm Hg based on a resting right heart catheterization (RHC). This threshold has been considered arbitrary and inconsistent with recent hemodynamic data of healthy individuals showing an average mean PA pressure of 14 $\pm$ 3.3 mm Hg, a value that was minimally influenced by age. This had led to a recent change in the cutoff for elevated pulmonary pressures as a mean PA pressure > 20 mm Hg during the most recent World Symposium in Pulmonary Hypertension.[10] Despite

[a] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, 1500 East Medical Center Drive, Cardiovascular Center, Floor 2, Ann Arbor, MI 48103, USA; [b] Division of Cardiovascular Medicine, Department of Internal Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, K14, Detroit, MI MI 48202, USA
* Corresponding author.
E-mail address: vmoles@med.umich.edu

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the recognition of this lower diagnostic threshold, PH-LHD continues to be defined as a mean PA $\geq$ 25 mm Hg and a pulmonary capillary wedge pressure (PCWP) > 15 mm Hg.[7] The definition of PH-LHD relies heavily on the accurate measurement of PCWP and special attention should be placed on measurements at end of expiration. In sinus rhythm, this corresponds to the mean of the A-wave.[7]

PH-LHD can be a result of several factors, including the passive transmission of elevated left-sided filling pressures, pulmonary vasculopathy, increased pulmonary blood flow, or a combination of these elements. Understanding the underlying pathophysiology may help in guiding medical management and selecting future therapeutic options. PH-LHD can be further divided into 2 categories based on PCWP and pulmonary vascular resistance (PVR): (1) isolated postcapillary pulmonary hypertension (IpcPH) when PCWP > 15 mm Hg and PVR < 3 WU; and (2) combined pre and postcapillary pulmonary hypertension (CpcPH) when PCWP > 15 and PVR $\geq$ 3 Wood units. Although previously the diastolic pressure gradient (DPG = PA diastolic–PCWP) was introduced to distinguish between IpcPH and CpcPH, this definition was found restrictive and exposed to interpretation, leading to PVR being subsequently reintroduced as part of the definition.[7] The importance of differentiating CpcPH from IpcPH is highlighted by a meta-analysis of 10 retrospective analyses showing that PVR was a strong predictor of survival.[11] Similarly, a recent large retrospective analysis also showed that PVR was a predictor of mortality and hospitalizations in HFpEF.[12]

As routine invasive RHC is often not performed as part of the diagnosis of HFpEF, the initial assessment of PH may rely heavily on an echocardiogram. Many studies which studied PH-HFpEF did so by using the echocardiogram to define PH. The probability of PH can be estimated based on the peak tricuspid regurgitation velocity and the presence of other supporting PH signs -RV/LV ratio >1.0, flattening of interventricular septum, right ventricular outflow tract notching or short acceleration time, elevated right atrial pressures based on IVC measurements- (**Table 1**), although most of these signs reflect an elevated PVR which not may necessarily be abnormal in PH-HFpEF.[13]

IS PULMONARY HYPERTENSION-HEART FAILURE WITH PRESERVED EJECTION FRACTION COMMON?

Lam and colleagues[5] reported an incidence of the PH of 83% based on echocardiographic data with a median right ventricular systolic pressure (RVSP) of 48 mm Hg in patients with HFpEF in Olmsted County. Also, the TOPCAT study showed that 36% of patients with had estimated systolic PA pressure of at least 35 mm Hg plus right trial pressure measured by echocardiogram.[14]

Strange and colleagues[3] performed a large observational population cohort study in Australia which showed that 9.1% of echocardiograms performed showed evidence of PH (estimated RVSP > 40 mm Hg). Based on clinical and echocardiographic data, patients were classified into in one of the 5 distinctive groups based on the updated classification at the time from the Third World Symposium on Pulmonary Hypertension.[15] PH-LHD was the most common type of PH diagnosed accounting for 68% of cases and an estimated incidence of 250 cases per 100,000. The presence of PH was significantly associated with poor survival. The mean survival rate for patients with PH-LHD was 4.3 $\pm$ 0.3 years. Interestingly, the survival for patients with PAH was better than those with PH-LHD, presumably because medical therapy was available.

WHAT ARE THE CLINICAL IMPLICATIONS OF PULMONARY HYPERTENSION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION?

The deleterious association of PH-LHD and survival were also assessed by Lam and colleagues[5] who used a random sample of patients with available echocardiographic data from Olmsted County, Minnesota. The increase in RVSP was coupled with increases in pulse pressure and echocardiography-derived PCWP, suggesting that age-associated blood vessel stiffness and diastolic dysfunction contribute to changes in pulmonary artery pressure. After adjusting for estimated PCWP, RVSP was higher in HFpEF compared to hypertensive individuals without heart failure. This suggests that beyond the postcapillary contribution of pulmonary venous congestion, a precapillary component may contribute to greater PH in HFpEF. The presence of PH defined by an RVSP above 35 mm Hg was strongly associated with mortality. Moreover, mortality was higher in those with an RVSP above the median of 48 mm Hg.

The presence of PH-HFpEF and RV dysfunction is associated with increased mortality.[16,17] Mohammed and colleagues[18] demonstrated in a community-based study that any degree of RV dysfunction was found in about 21–35% of patients -semi qualitatively or tricuspid annular plane systolic excursion (TAPSE) derived, respectively,

Table 1
Echocardiography probability of PH

Peak TR Velocity (m/sec)	Other Echocardiogram Findings Suggestive of PH	Echocardiographic Probability of PH
≤ 2.8 or unable to measure	Absent	Low
≤ 2.8 or unable to measure	Present	Intermediate
2.9–3.4	Absent	Intermediate
2.9–3.4	Present	High
>3.4	Not required	High

Supporting echocardiographic findings of PH: right ventricular to left ventricular basal diameter ratio> 1, flattening of the interventricular septum (eccentricity index > 1.1 in systole and/or diastole), right ventricular outflow tract Doppler acceleration time < 105 msec and/or midsystolic notching, early pulmonary regurgitation velocity > 2,2 m/sec, pulmonary artery diameter > 25 mm, inferior vena cava diameter > 21 mm with decreased respiratory variation (<50% with sniff or < 20% quiet inspiration, right atrial area at end of systole > 18 cm^2.

with HFpEF. Both RV dysfunction and elevated RVSP were associated with worse cardiovascular mortality and more frequent heart failure hospitalizations. Melenovsky and colleagues[19] described that 33% of patients with HFpEF had RV dysfunction -as defined by fractional area change < 35%- in a single-center study of patients who underwent RHC. Those with RV dysfunction had higher right heart filling pressures and more severe pulmonary vascular disease (higher PA pressures and PVR). Patients with HFpEF with RV dysfunction had higher mortality when compared to patients without RV dysfunction (median 2-year survival 56% vs 93%), and RV dysfunction was the strongest predictor for mortality (HR 2.4 CI 1.6–2.6).

HOW CAN PULMONARY ARTERIAL HYPERTENSION AND PULMONARY HYPERTENSION-HEART FAILURE WITH PRESERVED EJECTION FRACTION BE DIFFERENTIATED?

PH is usually suspected after an echocardiogram is performed in the setting of dyspnea on exertion and shows an elevated estimated RVSP. Although RHC is the definitive test of choice to define PH, echocardiography remains the screening test of preference for the initial evaluation and management of this condition. When findings such as decreased left ventricular systolic function or severe aortic or mitral valve pathology are present, the diagnosis of PH-LHD may be evident. On the other side, an elevated RVSP in the setting of preserved left ventricular ejection fraction may represent a diagnostic dilemma between PAH and PH-HFpEF. The echocardiogram is essential in generating an initial suspicion of the cause of PH and to predict hemodynamics (**Table 2**).[20]

The accuracy of echocardiography to diagnose PH was assessed in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), a large United States-based PH registry.[21] In patients who had both an echocardiogram and RHC performed on the same day, echocardiography underestimated RVSP in 29% of the cases, it overestimated RVSP in 31% of the cases and RVSP was within 10 mm Hg of RHC in 40% of the cases. This correlation did not change significantly whether the tests occurred on the same day or within 12 months. This study highlights the importance of invasive hemodynamic assessment when suspecting significant PH.

An assessment of the morphology of the RV can help predict hemodynamics and the cause of PH.[22] Raza and colleagues showed that an end-systolic RV base/apex ratio < 1.5 strongly correlates with an elevated PVR. In contrast, the RV base was twofold wider—end-systolic RV base/apex ratio > 2—than the apex in patients with PH-LHC. Of note, patients with CpcPH showed a low end-systolic RV base/apex ratio < 1.5, resembling those with PH due to pulmonary vascular disease. These findings are likely explained by the impact elevated RV afterload on the RV compared to elevated pressures due to passive left-sided pressure transmission.

Arkles and colleagues[23] demonstrated that a simple visual inspection of the right ventricular outflow tract (RVOT) Doppler provides a powerful insight into the hemodynamics in a diverse PH cohort. The presence of a midsystolic notch in the RVOT Doppler was highly sensitive and specific for the triad of markedly elevated PVR, decreased pulmonary vascular compliance, and RV dysfunction seen in patients with PH due to pulmonary vascular disease. On the other

Table 2
Echocardiographic findings that help differentiate precapillary PH vs postcapillary PH in patients with normal left ventricular systolic function

Precapillary PH (PAH)	Echocardiogram Parameter	Postcapillary PH (PH-HFpEF)
Usually normal or small	Left atrial size	Usually dilated
Bows right to left	Interatrial septum	Bows left to right
< 1.5	Right ventricle morphology (end-systolic RV base/apex ratio)	> 2
Present	RVOT Doppler midsystolic notch and/or short RVOT acceleration time < 80 ms.	Absent
Higher score	Prediction rule: LA diameter: < 3.2 cm = +1 LA diameter: > 4.2 cm = −1 RVOT notching and/or AT < 80 ms = +1 Lateral mitral E/e': > 10 = −1	Lower score
< 1	Mitral E/A ratio	> 1

Abbreviations: LA, left atrium; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-HFpEF: pulmonary hypertension due to heart failure with preserved ejection fraction; RV, right ventricle; RVOT, right ventricular outflow tract.

hand, PH in the absence of RVOT notching typically occurred in the setting of left heart congestion.

A simple prediction rule including left atrial diameter (+1 point for diameter < 3.2 cm and −1 point for diameter > 4.2 cm), RVOT Doppler notching assessment (+1 if present) or RVOT acceleration time (1+ if < 80 msec) and lateral mitral E/e' (−1 if > 10) accurately defines PH hemodynamics.[24] In this study of patients with normal left ventricular ejection fraction referred for the evaluation of PH, PVR increased stepwise with higher scores (score range −2 to +2). Negative scores argue strongly against PH due to a pulmonary vasculopathy. In addition, a negative score in conjunction with normal RVOT acceleration time and preserved RV function essentially excluded elevated PVR.

ARE THERE TREATMENT OPTIONS FOR PATIENTS WITH PULMONARY HYPERTENSION-HEART FAILURE WITH PRESERVED EJECTION FRACTION?

While pulmonary vasodilators are the standard of care in the treatment of PAH, results have not been consistently replicated in patients with PH-LHD; although these medications are sometimes tried in a patient with PH-HFpEF because of the significant symptoms and poor prognosis that is associated with this patient population. There have been trials using phosphodiesterase 5 inhibitors (PD5i), soluble guanylate cyclase (sGC) stimulator, endothelin receptor antagonists (ERA), and prostacyclin with mixed results.

Experimental models and human studies have shown that nitric oxide-dependent pulmonary vasodilation is impaired in heart failure and contributes to endothelial dysfunction.[25] These observations led to the investigation of PD5i and sGC as potential treatment options for PH-LHD.

Guazzi and colleagues studied sildenafil 50 mg three times a day for up to 12 months in a double-blind, randomized, placebo-controlled trial. Forty-four patients with HFpEF with echocardiographic evidence of PH (estimated RVSP $\geq$ 40 mm Hg) were enrolled, and sildenafil showed improvement in mean PA pressures, PVR, and RV function.[26] On the other hand, the RELAX study, which included patients with HFpEF with ejection fraction (EF) > 50%, failed to show a significant effect of sildenafil 60 mg three times a day in the primary endpoint of change in peak oxygen consumption at 24 weeks of therapy.[27] Secondary endpoints of 6-minute walk distance and a clinical rank score -composite of death, hospitalization and change in heart failure questionnaire- were also negative. Of note, RELAX did not require the presence of PH as part of the inclusion criteria. Hoendermis and colleagues studied the use of sildenafil 60 mg three times a day for 12 weeks in 52 patients with PH-HFpEF in a single-center, randomized, double-blind, placebo-controlled trial. There was no change in the primary endpoint of

mean pulmonary artery pressure at 12 weeks.[28] Interestingly, neither of these studies required an elevated PVR as part of the inclusion criteria and most patients had an IpcPH hemodynamic profile.

DILATE-1 evaluated the hemodynamic effect of a single dose of riociguat in patients with PH-HFpEF (EF > 50%, mean PA $\geq$ 25 mm Hg, and PCWP 15 mm Hg). There was no change in the primary endpoint of mean PA pressure compared to placebo. However, riociguat significantly increased stroke volume and decreased systolic blood pressure and RV end-diastolic area without changing PCWP, transpulmonary gradient, and PVR. As a follow-up, the phase IIb DYNAMIC study was designed to evaluate the efficacy, safety, and kinetics of riociguat in PH-HFpEF over 26 weeks with a primary endpoint of change in cardiac output. The results are not yet available. Pieske and colleagues[29] evaluated vericiguat in patients with EF $\geq$ 45% in the SOCRATES PRESERVED trial. The primary outcomes of this study were changed from baseline to week 12 in NT-proBNP and left atrial volume, which showed no improvement.

In patients with heart failure, plasma levels of endothelin-1 are elevated and associated with increased pulmonary pressure and higher risk for mortality.[30,31] Based on this observation, ERA have been evaluated as potential treatment options for heart failure.

The MELODY-1 study enrolled 63 patients with CpcPH confirmed by RHC and an EF >30%. In this phase II trial, patients were randomized to macitentan 10 mg daily or matching placebo for 12 weeks stratified by EF (<50% vs $\geq$ 50%). The median PVR was 5.8 WU, PCWP 20 mm Hg, and mean PA pressure 47 mm Hg; and 25% had EF <50%. At 12 weeks, the macitentan group showed no significant change in PVR, mean right atrial pressure, PCWP, and cardiac index. Notably, macitentan-treated patients were qualitatively more likely to experience fluid retention (10% treatment difference).[32] Bosentan, another ERA, was also previously evaluated in patients with HFrEF in the REACH-1 and ENABLE studies. Both of these trials were neutral for their primary outcome and were associated with worsening heart failure early in the treatment course.[33,34]

Levosimendan, an intravenous calcium sensitizer and inodilator, was evaluated in patients with PH-HFpEF, with mean PA $\geq$ 35 mm Hg, PCWP $\geq$ 20 mm Hg and EF $\geq$ 40%.[35] Six weeks of once-weekly infusions did not reduce the primary endpoint of peak exercise PCWP, but patients were noted to have a decrease in resting PCWP as well as improvement in 6-minute walk distance compared to placebo.

Currently, the CADENCE study (clinicaltrials.gov) is evaluating the effect of sotatercept—a first-in-class ligand trap for TGF-β superfamily ligands-in patients with PH-HFpEF and CpcPH. The rationale for performing this study comes from the PULSAR trial, which studied sotatercept in patients with PAH and showed a significant decrease in the primary endpoint of PVR, as well as improvements in prespecified secondary outcomes of 6-minute walk distance, NT-proBNP, and World Health Organization functional class.[36]

As seen, pulmonary vasodilators have shown mixed results in the treatment of PH-LHD with most results showing negative results and even signals of harm. Many of these trials studied pulmonary vasodilators in HFrEF. Of those who studied these medications in PH-HFpEF, the definition of PH was not uniform and not always based on invasive hemodynamics. Moreover, a distinction between IpcPH and CpcPH was not mandatory in most studies.

There has been significant interest in further understanding the cardiac and vascular changes leading to PH-HFpEF to help guide potential future therapies outside of traditional pulmonary vasodilators.[7] Vascular remodeling, metabolic syndrome oxidative stress, and fibrosis are all targets for future therapies. The vascular changes that occur in PH-HFpEF are different than what is seen in a patient with idiopathic PAH as well as patients with PH-HFrEF, and therefore respond differently to currently available therapeutic options. As well as arterial remodeling, there is significant venous remodeling and luminal narrowing that is similar to changes observed in pulmonary veno-occlusive disease.[37] The increased left atrial pressures and the associated back pressure leads causes barotrauma to the lung capillary and small arteries. These changes lead to a breakdown of the endothelial layer and increased permeability, resulting in gas exchange inefficiency, disrupted fluid filtration and reabsorption, and increased risk of pulmonary edema.[38] Patients with PH-HFpEF compared with PH-HFrEF have been found to have increased stiffness in the pulmonary circulation and vascular changes when compared to patients with the same pulmonary capillary wedge pressure leading to reduced pulmonary artery compliance (PAC = stroke volume/pulmonary artery pulse pressure).[39] Along with elevated pulmonary vascular changes and the uncoupling, further assessment of the RV shows diffuse fibrosis out of proportion to the degree of pulmonary hypertension in patients with PH-HFpEF.[40]

Table 3
Results of completed clinical trials PH-HFpEF

First Author/Study	Study Drug/Dose	Population (n)	Duration	Primary Outcome	Result
Guazzi et al,[26] 2011	Sildenafil 50 mg TID	HFpEF n = 44	12 months	PVR, RV performance, CPET	Improvement
Hoendermis et al,[28] 2015	Sildenafil 60 mg TID	HFpEF n = 52	12 weeks	mPAP vs placebo	No change
MELODY-1 [32]	Macitentan 10 mg daily	HF (EF> 30%) 75% HFpEF n = 48	12 weeks	Safety and tolerability	+10% fluid retention in active group
Burkhoff et al,[35] 2021	Levosimendan Weekly infusion (0.075–0.1 ug/kg/min for 24 hr)	HFpEF n = 37	6 weeks	Peak exercise PCWP	No change

Abbreviations: CPET, cardiopulmonary exercise testing; EF, ejection fraction; HF, heart failure; HFpEF, Heart failure with preserved ejection fraction; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV: right ventricular.

The variability of cardiac and vascular changes for each individual patient has made it more difficult to assess the efficacy of therapy. The importance of separating patients into specific phenotypes (i.e. IphPH, CpcPH, exercise PH, and so forth) has been an important step to further understanding the pathophysiology of the cardiac and vascular changes, defining prognosis, and serving as a basis for clinical trial design.[7]

To date, there are currently no FDA-approved therapies for PH-HFpEF. Diagnosis and management of the underlying comorbidities–sleep apnea, hypoxia, arrhythmias, hypertension, coronary artery, obesity disease, and diabetes mellitus others—remains a focus of treatment of patients with PH-HFpEF.

SUMMARY

PH is frequently seen in patients with HFpEF and is associated with significantly greater symptom burden and increased mortality. The echocardiogram remains the initial screening test for PH in HFpEF and can generate an initial impression of the type of PH present and RV function. The RHC is the test of choice to define PH-HFpEF, and also importantly, understand the underlying hemodynamic profile (IpcPH vs CpcPH). The use of pulmonary vasodilators in PH-HFpEF has been evaluated in multiple clinical trials with mixed results. There are currently no FDA-approved therapies for PH-HFpEF . There is a significant interest in finding an effective therapeutic option for this population and clinical trials are currently underway using novel mechanistic approaches in well-defined phenotypes. Improving the understanding of the different phenotypes and mechanisms of injury in each subset of patients with PH-HFpEF will be a critical step to improving the treatment in the future (Table 3).

CLINICS CARE POINT

- There are currently no FDA approved medical therapy for PH associated with HFpEF (PH-HFpEF).
- Differentiating between pulmonary arterial hypertension (PAH) and PH-HFpEF can be difficult and requires a high degree of suspicion. Referral to a tertiary center may be needed.

DISCLOSURE

The authors have nothing to disclose.

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