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Pulmonary Hypertension in the Context of Heart Failure With Preserved Ejection Fraction

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Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and frequently is associated with pulmonary hypertension (PH). HFpEF associated with PH may be difficult to distinguish from precapillary forms of PH, although this distinction is crucial because therapeutic pathways are divergent for the two conditions. A comprehensive and systematic approach using history, clinical examination, and noninvasive and invasive evaluation with and without provocative testing may be necessary for accurate diagnosis and phenotyping. After diagnosis, HFpEF associated with PH can be subdivided into isolated postcapillary pulmonary hypertension (IpcPH) and combined postcapillary and precapillary pulmonary hypertension (CpcPH) based on the presence or absence of elevated pulmonary vascular resistance. CpcPH portends a worse prognosis than IpcPH. Despite its association with reduced functional capacity and quality of life, heart failure hospitalizations, and higher mortality, therapeutic options focused on PH for HFpEF associated with PH remain limited. In this review, we aim to provide an updated overview on clinical definitions and hemodynamically characterized phenotypes of PH, pathophysiologic features, therapeutic strategies, and ongoing challenges in this patient population. CHEST 2021; 160(6):2232-2246

KEY WORDS: diastolic heart failure; heart failure with preserved ejection fraction; left heart disease; pulmonary hypertension; right ventricle

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and frequently is complicated by the development of pulmonary hypertension (PH). The prevalence of PH in HFpEF varies widely based on population, study design, the definition of PH, and diagnostic methods, with estimates ranging from 30% to 80%.[1] The hemodynamic and functional alterations that occur in the setting of abnormal cardiovascular structure and function contribute to the development

ABBREVIATIONS: AF = atrial fibrillation; CO = cardiac output; CpcPH = combined postcapillary and precapillary pulmonary hypertension; HFpEF = heart failure with preserved ejection fraction; IpcPH = isolated postcapillary pulmonary hypertension; LHD = left heart disease; LV = left ventricle; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PAC = pulmonary arterial compliance; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = right ventricle; sGC = soluble guanylyl cyclase; WU = Wood unit

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of PH.[2] HFpEF associated with PH is linked to dyspnea, ventilatory impairments, reduction in aerobic capacity, high symptom burden, an increase in hospitalizations, and higher mortality.[3] The present article on HFpEF associated with PH reviews the definition and classification, pathophysiology, challenges with diagnosis, and current and emerging treatment strategies.

Definition and Classification

The hemodynamic definition of PH resulting from left heart disease (LHD), also classified as World Health Organization group 2 PH, was proposed during the 6th World Symposium on Pulmonary Hypertension as a mean pulmonary artery pressure (mPAP) of $>$ 20 mm Hg and a pulmonary artery wedge pressure (PAWP) of $>$ 15 mm Hg as measured by right heart catheterization (RHC).[4] The lower threshold of mPAP is based on reference data in healthier control participants and was selected to harmonize with the new definition of pulmonary arterial hypertension (PAH).[5] Among those with recognized PH resulting from LHD, individuals are now stratified into isolated postcapillary pulmonary hypertension (IpcPH) and combined postcapillary and precapillary pulmonary hypertension (CpcPH) solely based on pulmonary vascular resistance (PVR) of $<$ 3 Wood units (WU) or $\geq$ 3 WU. CpcPH is associated with reduced right ventricle RV function and increased morbidity and mortality compared with IpcPH.[6] A recent analysis of 40,082 patients undergoing RHC in the US Veterans Affairs health care system found excess adjusted all-cause mortality began at a threshold of 2.2 WU, suggesting that even lower PVR values may be clinically relevant.[7] Finally, pulmonary arterial compliance (PAC; estimated as stroke volume to pulmonary artery [PA] pulse pressure ratio), and pulmonary arterial elastance, defined as systolic PA pressure to stroke volume ratio, are both impacted by left atrial hypertension and PVR. They may represent better the total RV afterload compared with precapillary parameters. Although they are associated with more significant RV dysfunction and are better predictors of outcomes in HFpEF associated with PH, they are not helpful in distinguishing IpcPH and CpcPH.[8]

Because these definitions and concepts rely heavily on hemodynamic definition, proper measurements of both pressures and cardiac output (CO) become essential. Although CO determined by the direct Fick method remains the gold standard measurement, the use of a metabolic cart for indirect calorimetry is not widespread in clinical practice. More often, indirect or so-called assumed Fick is used, although it has been demonstrated that its use may lead to inaccurate measures of CO in the setting of heart failure and PH.[9,10] Therefore, thermodilution technique is preferred if the direct Fick method cannot be performed and even in the setting of tricuspid regurgitation and low CO.[11]

Pathophysiologic Characteristics

Pulmonary Vasculature

In patients with HFpEF, abnormal myocardial active relaxation and increased passive stiffness of the left ventricle lead to elevation in left ventricular and thus left atrial pressures to maintain CO.[12] Left atrial pathologic features themselves may contribute further, exposing the lung vasculature to passive elevation in pressure.[13] Ultimately, elevated pressure, poor CO, or both leads to the development of a precapillary component resulting from pulmonary vasoconstriction, and in some cases, structural remodeling of the pulmonary veins, capillaries, and arteries occurs.[14,15]

Several factors contribute to the vascular pathologic features in HFpEF associated with PH (Fig 1, central figure). Left atrial hypertension causes stress failure of the alveolar-capillary junction with the development of pulmonary edema. The edema activates inflammatory mediators that increase endothelin 1 expression and decrease nitric oxide and natriuretic peptide activity. This also may lead to fibroblast proliferation, occlusion of the lumen, and thickening of the alveolar septa. The remodeling is reflected by impairment of gas exchange, contributing to dyspnea and hypoxemia.[16,17] Obokata et al,[18] in a prospective hemodynamic study of 38 patients with HFpEF and 20 control participants, found that the patients with HFpEF associated with PH displayed activation of endothelin and adrenomedullin neurohormonal pathways. The C-terminal pro-endothelin 1 and midregional proadrenomedullin levels were correlated strongly with mean PA pressure (r = 0.73 and r = 0.65, respectively; both $P < .0001$) and PAWP (r = 0.67 and r = 0.62, respectively; both $P <$ .0001) and inversely correlated with PAC (r = –0.52 and r = –0.43, respectively; both $P < .001$). Similarly, studying swine undergoing pulmonary vein banding, van Duin et al[19] recently found evidence of significant upregulation of the endothelin pathway that was associated with the transition from IpcPH to CpcPH. As mentioned above, left atrial hypertension also lowers PAC, making the vasculature stiff, increasing pulmonary pulse pressure, and indirectly increasing PVR.

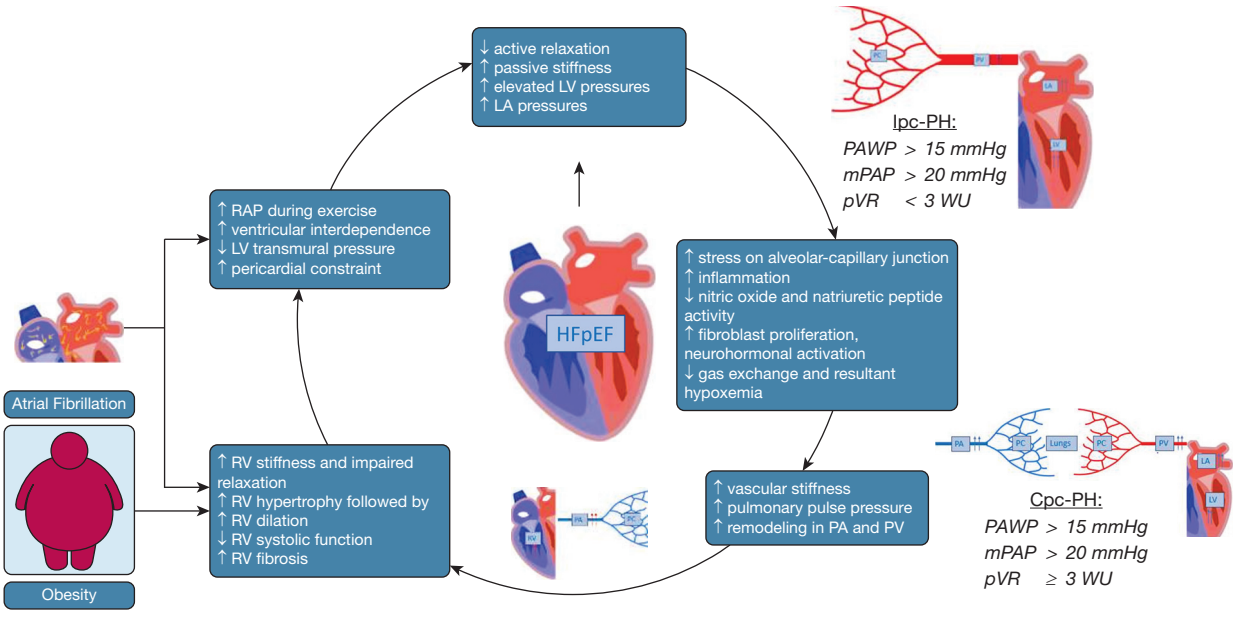

Figure 1 – *Diagram showing the pathophysiologic mechanisms in HFpEF associated with PH. CpcPH = combined postcapillary and precapillary pulmonary hypertension; HFpEF = heart failure with preserved ejection fraction; IpcPH = isolated postcapillary pulmonary hypertension; LA = left atrial; LAP = left atrial pressure; LV = left ventricle; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricle; WU = Wood unit.*

Furthermore, engorged lymphatics and edema may compress small distal lung arterioles, contributing to the precapillary component.[20]

The above factors and others eventually promote remodeling in the pulmonary arteries and veins with various combinations of intimal proliferation, medial hypertrophy, and adventitial thickening. In a landmark study of patients with HFpEF associated with PH, Fayyaz et al[21] found evidence of significant venous remodeling, with similar pathologic appearance to pulmonary venoocclusive disease. In keeping, it was venous and intermediate vessel changes that were associated more closely with pulmonary pressures than the arterial remodeling. Although presumed to be pathologic, it remains possible that the cited mechanisms instead are compensatory, that is, they "protect" the left heart from excessive preload. In a cohort free of cardiac disease, higher endothelin 1 levels at baseline were protective from future heart failure events and also were associated with smaller left ventricle (LV) size and higher LV ejection fraction.[22] These findings should be considered only hypothesis generating. Animal models of HFpEF and specifically HFpEF associated with PH recently were developed and ultimately may improve our understanding of the development of pulmonary vascular disease as well as heart dysfunction.[23,24]

RV

The function of the RV is likely the most important prognostic factor in HFpEF associated with PH.[25,26] RV diastolic dysfunction may occur early in the disease course. In a study of 24 compensated patients with HFpEF with preserved CO and mildly elevated pulmonary pressures and nine patients without heart failure symptoms who underwent RV pressure-volume measurement, increased RV stiffness and prolonged RV relaxation were present, although RV systolic function was preserved.[27] Later in the disease, overt RV systolic dysfunction can develop.[28] RV systolic function depends on both the afterload imposed on it from the pulmonary circulation and intrinsic myocardial contractility. PVR and PAC both contribute to increased resistive and pulsatile afterload.[29] Chronically elevated afterload results in RV hypertrophy as a compensatory mechanism. With sustained afterload, chamber dilation, tricuspid regurgitation, fibrosis, and loss of contractility, ultimately irreversible decrease in RV function ensues.[28] The processes of adaptation giving way to maladaptation and gene expression-related pathways that drive this transition largely are unknown. Comorbidities like atrial fibrillation (AF) and obesity frequently coexist in patients with HFpEF and may contribute to the inflammatory milieu, RV fibrosis, and even myocyte dysfunction. In 63 patients with HFpEF who underwent

RV septal endomyocardial biopsy sampling, those with marked obesity exhibited more depressed RV systolic sarcomere function, yet less passive myocyte stiffening.[30] Thus, although not well characterized, it seems certain that patient phenotypes may have an at-risk RV less able to compensate for increases in afterload.

RV and LV Interactions and AF

Ventricular interaction may play a significant role in the pathophysiologic features and functional limitations witnessed in HFpEF associated with PH, particularly in those with CpcPH.[31] LV transmural pressure, estimated as PAWP minus right atrial pressure, represents the true distending pressure of the LV (ie, preload). In HFpEF without PH and IpcPH, PAWP typically increases out of proportion to right atrial pressure during exertion, increasing the LV transmural pressure. However, patients with CpcPH demonstrate greater increases in right atrial pressure during exercise, enhanced ventricular interdependence, and a paradoxical reduction in LV transmural pressure. These changes, indicative of pericardial restraint, are associated with both impaired cardiac reserve and more significant reductions in aerobic capacity.[31] Worsening pulmonary vascular disease, right heart failure, and pericardial restraint also have been described in a subphenotype of HFpEF with permanent AF. Reduced left atrial compliance and impaired mechanics are associated with increasing burden of AF. AF and left atrial dysfunction seem to be strong promotors of PH in HFpEF.[32]

Diagnosis of HFpEF Associated With PH

The evaluation of a patient with suspected PH in HFpEF requires comprehensive clinical, echocardiographic, and hemodynamic assessments. A high degree of suspicion is necessary for the diagnosis of HFpEF associated with PH, which easily can be misdiagnosed as PAH.[2] Factors associated with PH resulting from LHD include the presence of AF, left atrial enlargement, age older than 60 years, coronary artery disease, and BMI of > 30 kg/m^2 (Table 1), and these factors help to determine the pretest probability of PH resulting from LHD. The physical examination and chest radiograph provide signs of fluid retention or signs of RV failure. Transthoracic echocardiography serves as an excellent screening tool and is the first step in the evaluation of patients suspected of PH. Although elevated PA systolic pressures values derived from Doppler echocardiography correlate with the presence of elevated pulmonary pressures, the accuracy of pulmonary artery systolic pressure estimates are variable between studies.[33] Better accuracy can be observed when using modal frequency for velocity estimates, optimizing insonation angle, and resisting the temptation of

TABLE 1] Pretest Probability of LHD Phenotype vs Pulmonary Arterial Hypertension or Precapillary PH

Feature	High Probability	Intermediate Probability	Low Probability
Age, y	> 70	60-70	< 60
Obesity, systemic hypertension, dyslipidemia, glucose intolerance or diabetes	> 2 factors	1-2 factors	None
Previous cardiac intervention[a]	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural LHD	Present	No	No
ECG	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade > 2 mitral flow	No LA dilation; grade < 2 mitral flow	No LA dilation; E to e' ratio < 13
CPET	Mildly elevated V'_E to V'_{CO2} ratio slope; EOV	Elevated V'_E to V'_{CO2} ratio slope or EOV	High V'_E to V'_{CO2} ratio slope; no EOV
Cardiac MRI	LA strain or LA to RA ratio > 1	…	No left heart abnormalities

Reproduced with permission of the European Respiratory Society from *Eur Respir J.* 2019;53(1):1801897. DOI: 10.1183/13993003.01897-2018. Published January 24, 2019.[36] © 2021 European Respiratory Society. CPET = cardiopulmonary exercise testing; E/e' = early mitral inflow velocity to mitral annular early diastolic velocity ratio; EOV: exercise oscillatory ventilation; LA = left atrium; LBBB = left bundle branch block; LHD = left heart disease; LVH = left ventricular hypertrophy; PH = pulmonary hypertension; RA = right atrium; RV = right ventricle; V'_E/V'_{CO2} = minute ventilation to CO_2 production ratio.
[a]Coronary artery, valvular surgical, or nonsurgical procedures, or a combination thereof, including percutaneous interventions.

estimating pressures in the presence of an incomplete signal.[34] Pulmonary function testing can identify associated lung disease and aid in PH classification. Although not always part of the standard evaluation, cardiopulmonary exercise testing may be useful diagnostically to differentiate subtypes of PH, because higher ratio of minute ventilation to volume of exhaled carbon dioxide (Ve/VCO_2) slope is associated with more significant precapillary disease, whereas the presence of exercise oscillatory ventilation, defined as cyclic fluctuations in ventilation at rest that persist during effort lasting $\geq$ 60% of the exercise duration, with an amplitude of $\geq$ 15% of the average resting value, is more common in IpcPH.[35] Individuals with CpcPH should be ruled out for chronic thromboembolic disease and other conditions associated with precapillary disease as guided by history, physical examination, and diagnostic evaluation.

Although transthoracic echocardiography is the recommended screening tool, RHC remains the gold standard for diagnosis and proper phenotyping.[37] Most importantly, PAH must be excluded given the disparate therapeutic strategies between it and HFpEF associated with PH. The key hemodynamic differentiator is PAWP, which typically is measured at end-expiration during normal respiration when intrathoracic pressure is closest to zero.[38] In situations of severe lung disease and perhaps morbid obesity, large respiratory swings may be present, and averaging over the respiratory cycle may be more appropriate, although in these two populations, proper measurement remains a point of debate.[39,40] Whenever the PAWP tracing morphologic features are atypical or precapillary PH is suspected clinically despite a measured PAWP of $>$ 15 mm Hg, a PAWP oxyhemoglobin saturation content should be analyzed.[41] A truly wedged catheter will yield a oxyhemoglobin saturation reflective of the postcapillary pulmonary bed, typically $>$ 90% to 95%. Lower values should prompt repeat attempts to wedge, including alternate vascular areas or consideration of direct LV measurement.

Despite the importance of an accurately measured PAWP, a single variable may be inadequate to confirm a diagnosis of PH resulting from LHD. This may be particularly relevant when considering the new and lower mPAP threshold to diagnosis PH, where the elderly and those with chronic heart and lung disease may be overrepresented among men and women with mildly elevated mPAP (from 19 to 24 mm Hg).[36] As such, particularly among individuals with mild PH, the pretest probability for PH resulting from LHD should be higher. With the use of diuretics and afterload reduction, it is possible to lower PAWP into the normal range despite the presence of significant LHD. This has led some experts to suggest that a diagnostic RHC be performed before volume status optimization.[11] When an intermediate to high probability of PH resulting from LHD exists, but hemodynamics meet criteria for a precapillary disease, additional testing should be considered. Figure 2 outlines a suggested algorithm from the 6th World Symposium on Pulmonary Hypertension.[38] Given the practical and technical challenges with exercise, this most recent position statement recommends a fluid challenge to detect occult left heart disease, specifically when differentiating group 1 from group 2 PH. A PAWP of $>$ 18 mm Hg immediately after the administration of 500 mL of normal saline over 5 min (or weight-based dosing of 7 mL/kg) is considered abnormal and suggestive of PH resulting from LHD.[38,42,43] However, some maintain that exercise testing is more a relevant physiologic stressor, and therefore, at expert centers, cycle ergometry may be performed as an alternative, with a cutoff of PAWP $\geq$ 25 mm Hg during supine exercise (or $\geq$ 20 mm Hg during upright exercise) generally accepted as representing the presence of LHD.[44] However, it should be noted that pressures obtained during exercise may vary significantly depending on how the PAWP is measured with respect to the respiratory cycle.[37] The position statement from the European Respiratory Society recommends averaging over the respiratory cycle during exercise,[45] although typically we report both values in cases of substantial respiratory swings. The multipoint slope of PAWP and CO is an alternative measure to discriminate between occult LHD and normal left-sided response to exercise, with $>$ 2 mm Hg/L/min being considered abnormal.[46] Baratto et al[47] recently evaluated the impact of respiratory pressure swings on three exercise hemodynamic criteria for HFpEF, noting discordant results in 30% of patients. The authors concluded that equivocal diagnoses of HFpEF may be limited by adopting end-expiratory PAWP to CO ratio slope. Additional prospective studies are needed to define the optimal diagnostic approaches.

Therapeutic Strategies

The significant gaps in understanding the complex pathobiological processes and comorbidities that complicate or drive the development and progression of PH have rendered the search for effective therapies particularly difficult. Furthermore, PH may represent a

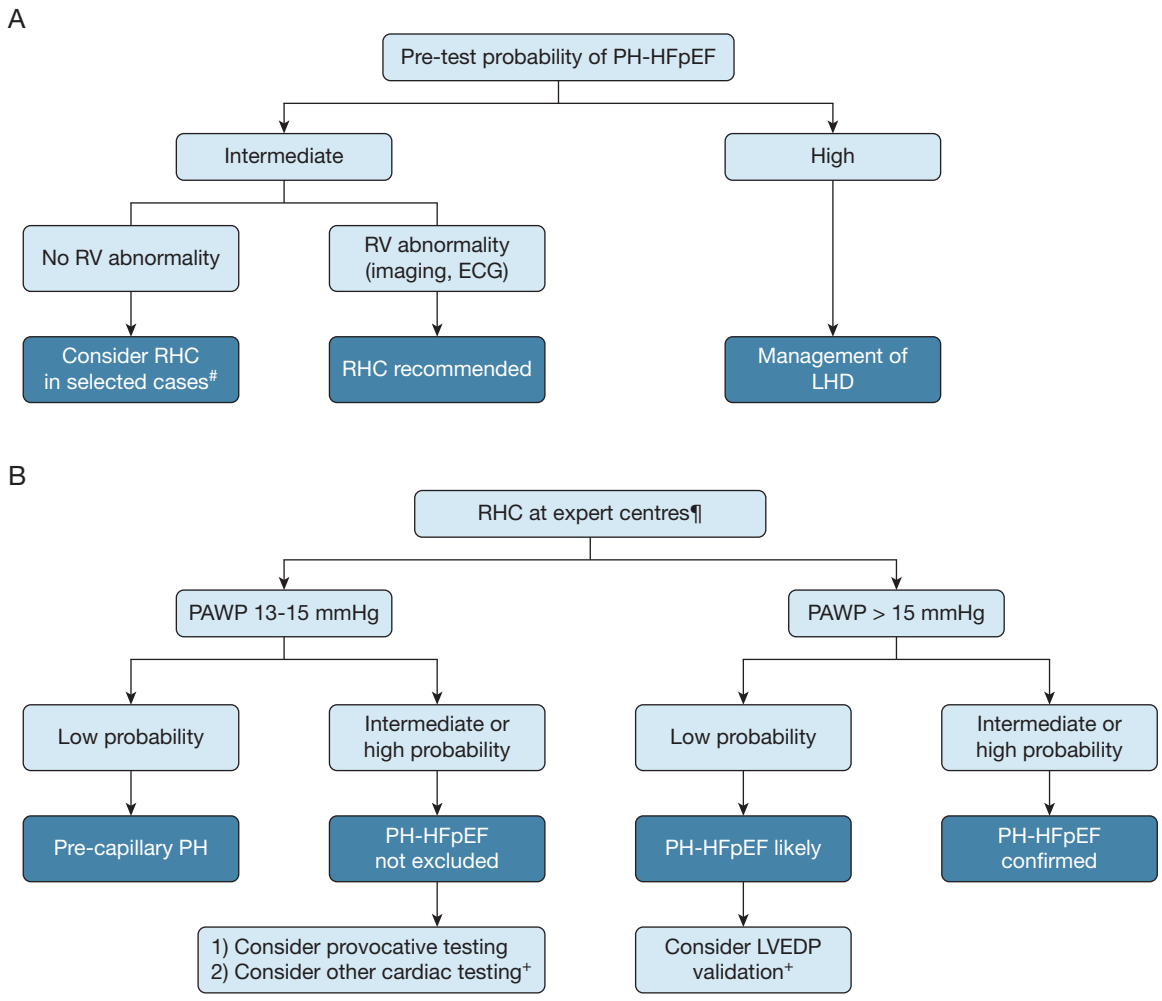

Figure 2 – *A-B, Flow charts showing the hemodynamic assessment of PH resulting from HFpEF. A, Pretest probability of PH resulting from LHD is based on the features presented in Table 1. RHC is recommended in intermediate probability when risk factors of pulmonary arterial hypertension or CTEPH are present, if evidence exists of RV abnormality, or both. If the probability is high, patients should be managed according to recommendations for LHD. B, For the assessment of PH, RHC should be performed at expert centers. In patients with intermediate or high probability (Table 1) and PAWP between 13 and 15 mm Hg, HFpEF associated with PH is not excluded; provocative testing should be considered. #For patients with systemic sclerosis, risk factors for CTEPH, unexplained dyspnea, or both. +If PAWP of > 15 mm Hg, LVEDP validation should be considered. CTEPH = chronic thromboembolic PH; HFpEF = heart failure with preserved ejection fraction; LHD = left heart disease; LVEDP = left ventricular end-diastolic pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; RHC = right heart catheterization; RV = right ventricle. Reproduced with permission of the European Respiratory Society from Eur Respir J. 2019;53(1):1801897. DOI: 10.1183/13993003.01897-2018. Published January 24, 2019.[36] © 2021 European Respiratory Society.*

marker of disease severity, rather than an optimal target for therapy. Select clinical trials with biologic plausibility to treat HFpEF associated with PH are summarized in Table 2.[48–60] Currently, no pharmacologic agents exist that are approved specifically to target PH in the setting of HFpEF, a result of disappointing results from these numerous studies. Loop diuretics for relief of volume overload and concomitant treatment of comorbidities are the mainstays of therapy in HFpEF and, therefore, HFpEF associated with PH. In addition to normalization of intracardiac and pulmonary pressures and symptom relief, diuresis associated with increases in PAC reduce pulsatile loading to the RV. The use of pulmonary artery monitoring devices may be particularly useful to achieve and maintain euvolemia. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial was a prospective, randomized controlled trial that enrolled 550 patients with heart failure with both reduced and preserved ejection fraction. Patients randomized to hemodynamic-guided care received substantially more medication titrations (principally diuretics) and

TABLE 2] Representative Clinical Trials of Heart Failure With Preserved Ejection Fraction

Trial	Intervention	Sample Size and Duration	Inclusion Criteria	Study Design	End Points	Results
Guazzi et al,[49] *Circulation* (2011)[a]	Sildenafil vs placebo	N= 44; 6 and 12 mo	LVEF ≥ 50%, sinus rhythm, PASP ≥ 40 mm Hg	Prospective, double-blind, randomized, single-center study	Hemodynamics and RV function on echo	Sildenafil: reductions in mPAP, PVR, RAP, and PAWP with improvements in TAPSE and QOL
Redfield et al,[50] *JAMA* (2013; RELAX)	Sildenafil vs placebo	N = 216, 24 wk	pVO_2 < 60% normal, NT-proBNP > 400 pg/mL, or NT-proBNP < 400 pg/mL with PAWP > 20 mm Hg	Prospective, randomized, multicenter, double-blind, placebo-controlled study	Change in pVO_2 after 24 wk (primary)	Sildenafil: −0.20 mL/kg/min vs baseline (IQR, −0.70 to 1.00) Placebo: −0.20 mL/kg/min vs baseline (IQR, −1.70 to 1.11; *P* = .90) at 24 wk
Abraham et al,[48] *Circ Heart Fail.* (2014; CHAMPION, HFpEF analysis)	CardioMEMS (pulmonary artery pressure monitor) sensor-guided management vs standard HF management in HFpEF	N = 119, mean follow-up of 17 mo	NYHA class III, HF hospitalization in previous 12 mo	Prospective, randomized, multicenter, single-blind (post hoc analysis)	Rate of HF hospitalizations after 6 mo	Incidence rate ratio for heart failure hospitalization after 6 mo 0.54 for LVEF > 40% in treatment vs control subject (*P* < .0001)
Bonderman et al,[54] *Chest* (2014; (DILATE-1)[a]	Riociguat vs placebo	N = 477, 6 h	LVEF > 50%, mPAP ≥ 25 mm Hg, PAWP > 15 mm Hg (at rest)	Prospective, randomized, multicenter, double-blind, placebo-controlled study	Peak decrease in mPAP, change in stroke volume, RV end-diastolic area	Riociguat: peak decrease in mPAP 10 mm Hg vs 11 mm Hg with placebo (*P* = .6); +9 mL in stroke volume vs placebo (*P* = .04)
Redfield el al,[55] *N Engl J Med* (2015 (NEAT-HFpEF)	Isosorbide mononitrate vs placebo (6-wk dose-escalation regimen of isosorbide mononitrate with subsequent crossover to the other group for 6 wk)	N = 110; 12 wk	LVEF ≥ 50% and objective evidence of heart failure	Prospective, multicenter, double-blind, crossover study	Daily activity level, quantified as the average daily accelerometer	Isosorbide mononitrate: less activity; no improvement in QOL or submaximal exercise capacity

(Continued)

TABLE 2] *(Continued)*

Trial	Intervention	Sample Size and Duration	Inclusion Criteria	Study Design	End Points	Results
Borlaug et al,[56] *JACC* (2015)	IV sodium nitrite vs placebo compared via invasive hemodynamics and measured gas exchange 15 min after administration	N = 28; 15 min after drug administration	LVEF ≥ 50% and symptoms of HF, PAWP > 15 mm Hg at rest or ≥ 25 mm Hg with exercise	Prospective, single-center, double-blind, placebo-controlled, parallel-group study	Exercise PAWP, mean PAP, mPAP to CO ratio, LVSW sodium nitrite infusion acutely	IV inorganic nitrite led to acute attenuation of PAWP rise with exercise, reduction in exercise-induced PH, and improved CO reserve
Simon et al,[57] *JCI Insight* (2016)[a]	Aerosolized sodium nitrite	N = 36; 15-60 min	WHO group I, II, and III PH; exploratory for group 2 PH (PH-HFpEF); change in PVR for group 1 and group 3 PH	Prospective, open-label safety and efficacy study	Baseline hemodynamics before and after inhaled NO as well as at 15-min intervals after 45 mg and then 90 mg aerosolized sodium nitrite	Aerosolized sodium nitrite was well tolerated, and in HFpEF associated with PH (n = 10). Compared with other PH groups, patients with HFpEF associated with PH experienced greatest decrease in PAWP, RAP, RV, and PAP. Pulmonary artery compliance also improved in patients with HFpEF associated with PH.
Borlaug et al,[58] *Circ Res* (2016)	Nebulized inhaled sodium nitrite 90 mg vs placebo	N = 26; hemodynamics at rest, then after 5 min of exercise, then 5 min after intervention	HFpEF (LVEF ≥ 50%, PAWP at rest > 15 mm Hg or with exercise ≥ 25 mm Hg)	Prospective, randomized, single-center, double-blind, placebo-controlled, parallel-group study	Primary end point: PAWP during exercise; secondary end points included changes in PAWP and other hemodynamic measurements	Nebulized inhaled nitrite reduced biventricular pressures and PAPs at rest and during exercise

(Continued)

TABLE 2] *(Continued)*

Trial	Intervention	Sample Size and Duration	Inclusion Criteria	Study Design	End Points	Results
Vachiéry et al,[53] *Eur Respir J* (2018; (MELODY-1)[a]	Macitentan vs placebo	N = 63, median treatment duration of 12 vs 12.1 wk in macitentan vs placebo groups	LVEF ≥ vs < 50% (stratified by LVEF) and CpcPH confirmed by RHC with mPAP > 25 mm Hg, PAWP > 15 mm Hg and < 25 mm Hg, and PVR at rest ≥ 3 WU with DPG ≥ 7 mm Hg	Prospective, randomized, multicenter, double-blind, placebo-controlled study	Composite primary end point of significant fluid retention or worsening in NYHA functional class from baseline up to end of trial, safety, PVR	Macitentan: associated with no change in PVR, mean RAP, or PAWP compared with placebo. Statistically nonsignificant but numerically greater number of adverse events and serious adverse events with macitentan vs placebo.
Pieske et al,[59] *Eur Heart J* (2017; (SOCRATES-PRESERVED)	Vericiguat vs placebo	N = 477, 12 wk	LVEF > 45%	Prospective, randomized, double-blind, placebo-controlled dose-finding study	Change from baseline NT-proBNP and left atrial volume at 12 wk	Vericiguat: no significant change in NT-proBNP or LAV at 12 wk vs placebo, associated with improved QOL
Reddy et al,[60] *Circ Res* (2019; (albuterol in HFpEF)	Inhaled albuterol vs placebo	N = 30, single episode of invasive hemodynamic exercise testing	LVEF ≥ 50%, resting end-expiratory PAWP ≥15 or exercise PAWP ≥ 25 mm Hg at 20 W workload	Prospective, randomized, double-blind, parallel-group, placebo-controlled trial	Exercise PVR, resting PVR, rest and exercise PAWP, other measures of RV reserve	Albuterol: reduction in exercise PVR −0.6 ± 0.5 WU vs +0.1 ± 0.7 WU (P = .003). Albuterol also improved PA compliance, arterial elastance, RV-PA coupling, and cardiac output.
Armstrong et al,[51] *JAMA* (2020; (VITALITY-HFpEF)	Vericiguat, uptitrated to 15-mg (n = 264) or 10-mg (n = 263) daily oral dosages compared with placebo (n = 262) and randomized 1:1:1	N = 789, 24 wk	LVEF ≥ 45%, NYHA class II-III, within 6 mo of a recent decompensation, and elevated natriuretic peptides	Phase 2b randomized, double-blind, placebo-controlled, multicenter trial	PLS of the KCCQ	Vericiguat: no improvement of PLS of KCCQ compared with placebo; no change in 6-min walk distance

(Continued)

TABLE 2] *(Continued)*

Trial	Intervention	Sample Size and Duration	Inclusion Criteria	Study Design	End Points	Results
Udelson et al,[52] *JAMA* (2020; (CAPACITY-HFpEF)	40 mg praliciguat daily or placebo	N = 196, 12 wk	LVEF ≥ 40%, impaired peak $\dot{V}o_2$, and at least two conditions associated with NO deficiency	Randomized, double-blind, placebo-controlled, phase 2 trial	Change from baseline in peak $\dot{V}o_2$ in patients who completed at least 8 wk of assigned dosing	Praliciguat: no difference in peak $\dot{V}o_2$ or 6-min walk distance

CO = cardiac output; CpcPH = combined postcapillary and precapillary pulmonary hypertension; DPG = diastolic pulmonary gradient; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAV = left atrial volume; LVEF = left ventricle ejection fraction; LVSW = left ventricular stroke work; mPAP = mean pulmonary artery pressure; NEAT-HFpEF = Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction; NO = nitric oxide; NT-proBNP = N-terminal (NT)-pro hormone brain natriuretic peptide; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PLS = physical limitation score; $p\dot{V}o_2$ = peak $\dot{V}o_2$; PVR = pulmonary vascular resistance; QOL = quality of life; RAP = right atrial pressure; RHC = right heart catheterization; RV = right ventricle; SOCRATES-PRESERVED = Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients With Heart Failure and Preserved Ejection Fraction Suffering From Worsening Chronic Heart Failure; TAPSE = tricuspid annular plane systolic excursion; WHO = World Health Organization; VITALITY-HFpEF = Patient-reported Outcomes in Vericiguat-treated Patients With HFpEF8; WU = Wood unit.

[a]Trial with inclusion criteria than include PH.

experienced a significant reduction in heart failure hospitalizations compared with control participants. For one of the first times, patients with HFpEF and heart failure with reduced ejection fraction showed similar benefit.[48] A postmarketing surveillance study of more than 2,000 patients (34% with HFpEF associated with PH) yielded similar results.[61]

The role of the mineralocorticoid receptor antagonist spironolactone in HFpEF was studied in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial.[62] Although the trial failed to meet its primary end point, perhaps because of enrollment irregularities in Russia and Georgia, a reduction in heart failure hospitalizations was noted.[63] Animal and preliminary human data in PAH suggest that aldosterone antagonists may reduce pulmonary vasoconstriction by attenuating the adverse effects of hyperaldosteronism on endothelin type-B receptor function in pulmonary endothelial cells.[64] Whether this may add particular benefit in HFpEF associated with PH is unknown. In addition, a large cohort of veterans with PH suggested that a mortality benefit with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockade. This included veterans with LHD; however, HFpEF was not differentiated specifically in this cohort.[65]

In addition to the optimization of filling pressures, management of the underlying comorbidities like AF, coronary artery disease, systemic hypertension, metabolic syndrome, and diabetes mellitus is necessary. These factors are relevant prognostically and may be associated with unique and targetable phenotypes.[66,67] The presence of underlying valvular heart disease should be investigated and considered as a potential therapeutic target. AF is highly comorbid with HFpEF, with the combination often exacerbating the likelihood of hospitalization. Rhythm control strategies including catheter ablation may offer benefit over rate control, although data from a prospective, randomized controlled trial are needed.[68] With the increasing prevalence of an obesity and metabolic HFpEF phenotype, weight loss management and aerobic exercise are critical interventions and both have been shown to improve exercise tolerance and to reduce body weight in HFpEF.[69]

PAH-Targeted Therapies

Studies of pulmonary vasodilators in HFpEF associated with PH largely have been disappointing. Although phosphodiesterase 5 inhibitors have proven efficacious

in PAH, their role in HFpEF associated with PH remains unproven. In a prospective placebo-controlled single-center trial of 44 patients with HFpEF associated with PH defined by elevated pulmonary artery systolic pressure of > 40 mm Hg and severe RV dysfunction, sildenafil use compared with placebo showed improvement in pulmonary pressures, RV function, and RV dimensions at 6 months.[49] Although it was not enriched for CpcPH, the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) study of sildenafil use in patients with HFpEF did not improve mPAP, PAWP, CO, exercise tolerance, or maximal oxygen consumption.[70,50] In a post hoc analysis of the trial, sildenafil failed to reduce RV afterload.[71] Similar results were obtained in other studies predominately of IpcPH.[70] In a randomized double-blind placebo-controlled trial of 222 patients (108 with CpcPH and 80 with IpcPH) with HFpEF associated with PH related to successfully corrected (at least 1 year before enrollment) valvular heart disease, sildenafil treatment was associated with worse clinical outcomes compared with placebo.[72] The phosphodiesterase-5 inhibition in patients with heart failure with preserved ejection fraction and combined post- and pre-capillary pulmonary hypertension (PASSION) trial evaluating the effects of tadalafil on HFpEF and CpcPH currently is underway.

Although phosphodiesterase 5 inhibitors have failed to show benefit in undifferentiated HFpEF associated with PH and remain under investigation in CpcPH, another class of medications affecting the same downstream signaling pathways also has been evaluated. Whereas phosphodiesterase 5 inhibitors prevent the breakdown of cyclic guanosine monophosphate—a vasodilatory and antiproliferative molecular signal—the soluble guanylyl cyclase (sGC) stimulators function to directly increase sGC levels in the vasculature and other tissues. The acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1) trial evaluated the role of the sGC stimulator riociguat compared with placebo in 39 patients with HFpEF associated with PH and notably included five patients with CpcPH. No significant change in mPAP or PVR at 6 h was noted in this proof-of-concept study. Subsequent large, prospective randomized trials of sGC stimulators have shown no benefit in patients with undifferentiated HFpEF.[51,52,73] Finally, several investigations targeting the endothelin pathway have been reported. A study of the selective endothelin type A receptor sitaxsentan in 192 patients with HFpEF did not meet statistical significance for end points including New York Heart Association functional class, heart failure hospitalizations, measures of diastolic function, or quality-of-life questionnaire scores. However, a significant increase in median treadmill time was observed.[74] The Clinical Study to Evaluate the Safety and Tolerability of Macitentan in Subjects With Combined Pre- and Post-capillary Pulmonary Hypertension (CpcPH) Due to Left Ventricular Dysfunction (MELODY-1) study evaluated the acute role of the endothelin receptor antagonist macitentan in patients with CpcPH identified by diastolic pressure gradient of ≥ 7 mm Hg and PVR of ≥ 3 WU. The trial was powered to evaluate safety end points. At 12 weeks, more adverse events were noted with macitentan compared with placebo, with no improvement in PVR or mean right atrial pressure.[53] Unfortunately, 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) trial, which specifically enrolled patients with HFpEF and pulmonary vascular disease or RV dysfunction, was stopped prematurely (ClinicalTrials.gov Identifier: NCT03153111). At present, PAH-specific therapies should be avoided in HFpEF associated with PH.[38] This recognition is relevant given relatively recent real-world evidence suggesting that PAH-specific therapies may be prescribed nearly as frequently for PH resulting from LHD as PAH and are used more frequently than might be assumed for PH resulting from LHD in the rare setting of complex and multifactorial causes.[75]

Early Phase or Investigational Therapies

Several ongoing pharmacologic and device therapies are being studied in HFpEF associated with PH. Early-phase studies of intra-atrial septal devices have shown promise in exercise-induced HFpEF, but have not specifically enrolled patients with HFpEF associated with PH.[76,77] In early studies, intra-atrial septal devices were associated with reduction in PVR, pulmonary arterial elastance, and improvement in PAC at 6 months.[77] In an open-label study, the use of an intra-atrial septal device was associated with sustained improvements in New York Heart Association functional class ($P < .001$), quality of life ($P < .001$), and 6-min walk distance ($P < .01$).[78] Whether those with CpcPH may be at higher risk of RV dilation or dysfunction after these therapies remains unknown. In a study of 37 patients with group 2 PH

with heart failure with ejection fraction of at least 40%, New York Heart Association II or III heart failure, once weekly levosimendan compared with placebo did not reduce the primary end point of exercise PAWP significantly (–1.4 mm Hg; 95% CI, –7.8 to 4.8; $P = .65$). However, levosimendan reduced PAWP measured across all exercise stages (–3.9 ± 2.0 mm Hg; $P = .047$) and resulted in a 29.3-m (95% CI, 2.5-56.1 m; $P = .033$) improvement in 6-min walk distance compared with placebo.[79] Metformin currently is being studied in a phase 2 trial for HFpEF associated with PH (ClinicalTrials.gov Identifier: NCT03629340) based on several lines of evidence, including improved heart failure outcomes in patients with type 2 diabetes in several large observational cohorts, decrease in cardiac work associated with reduced myocardial glucose uptake and fatty acid oxidation, and improvements metabolism in both skeletal muscle and pulmonary vascular smooth muscle via upregulation of the SIRT3-AMPK-Glut4 pathway.[80] In keeping with the metabolic mechanisms contributing to HFpEF, two large, randomized trials (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [EMPEROR-Preserved] [ClinicalTrials.gov Identifier: NCT03057951] and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [DELIVER] [ClinicalTrials.gov Identifier: NCT03619213]) are evaluating the role of SGLT2 inhibitors in HFpEF, results of which could inform the management of HFpEF associated with PH.

Nitrite, which is reduced to nitric oxide by hemoglobin, currently is being studied in an oral formulation for HFpEF associated with PH (ClinicalTrials.gov Identifier: NCT03015402), having shown promise in an inhaled formulation in HFpEF associated with PH predominately through improvement in PAC. However, a broader study of HFpEF (uncontrolled for PH) did not show improvement in exercise capacity as assessed by cardiopulmonary exercise testing and 6-min walk distance.[81] Early-phase studies of oral milrinone also have been conducted that suggest improvement in exercise hemodynamics and improved quality-of-life measures.[82] Finally, PA denervation therapy in CpcPH was studied in the Pulmonary Arterial Denervation in Patients With Pulmonary Hypertension Associated With the Left Heart Failure (PADN-5) study, in which approximately 40% of patients had received a diagnosis with HFpEF. Compared with sildenafil alone, PA denervation resulted in a significant increase in 6-min walk distance and lower PVR.[83] Additional studies of this potentially promising therapy, such as Treatment of Pulmonary Hypertension Group II Study (TROPHY-II) (ClinicalTrials.gov Identifier: NCT03611270) are underway.

Conclusions

In HFpEF, the development of PH is recognized as an important contributor to morbidity and mortality. Differentiation from PAH can be subtle and requires careful attention during diagnostic evaluation. Recent studies have paved the way for a better understanding of the pathobiology and relevant diagnostic and prognostic methodologies. Those therapeutic interventions aimed at targeting elevated pulmonary pressures largely have been disappointing, but novel therapeutic strategies currently are being studied.

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