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

Chakradhari Inampudi M.D.[1](Inampudi@musc.edu), Daniel Silverman M.D[1] (Silvermd@musc.edu), Marc A. Simon M.D, M.S.[2] (Marc.Simon@ucsf.edu), Peter J. Leary M.D., Ph.D.[3](Learyp@uw.edu), Kavita Sharma, M.D.[4](Ksharma8@jhmi.edu), Brian A. Houston M.D[1](houstobr@musc.edu), Jean-Luc Vachiery M.D.[5](Jeanluc.vachiery@erasme.ulb.ac.be), Francois Haddad M.D.[6](Fhaddad@stanford.edu), Ryan J Tedford, M.D[1](TedfordR@musc.edu)

1. Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC USA
2. Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, CA USA
3. Department of Medicine, University of Washington, Seattle, Washington USA
4. Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD USA
5. Département de Cardiologie Cliniques Universitaires de Bruxelles-Hôpital Erasme, Brussels, Belgium.
6. Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford CA USA

First Author:

Chakradhari Inampudi M.D.
Assistant Professor Medicine
30 Courtenay Drive, MSC592
Charleston, SC 29425, USA
Email: Inampudi@musc.edu
Twitter Handle: @chakri0012

Correspondence to:

Ryan J. Tedford, MD, FACC, FAHA, FHFSA
Dr. Peter C. Gazes Endowed Chair in Heart Failure
Professor of Medicine/Cardiology

Chief, Heart Failure
Medical Director, Cardiac Transplantation
Director, Advanced Heart Failure & Transplant Fellowship Training Program
Medical University of South Carolina (MUSC)
30 Courtenay Drive
BM215, MSC592
Charleston, SC 29425
(843) 792-3355 *office*
(843) 876-4990 *fax*
Email: TedfordR@musc.edu
Twitter Handle: @RyanTedfordMD

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Key Words/Terms: Heart failure with Preserved Ejection Fraction, Pulmonary Hypertension, Right Ventricle; Diastolic Heart Failure; Left Heart Disease

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and is frequently associated with pulmonary hypertension (PH). PH-HFpEF may be difficult to distinguish from pre-capillary forms of PH, though this distinction is crucial as therapeutic pathways are divergent for the two conditions. A comprehensive and systematic approach utilizing history, clinical exam, non-invasive and invasive evaluation with and without provocative testing may be necessary for accurate diagnosis and phenotyping. Once diagnosed, PH-HFpEF can be subdivided into isolated post-capillary pulmonary hypertension (IpcPH) and combined post- and pre-capillary pulmonary hypertension (CpcPH) based on the presence or absence of elevated pulmonary vascular resistance (PVR). 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 pulmonary hypertension for PH-HFpEF remain limited. In this review, we aim to provide an updated overview on clinical definitions and hemodynamically characterized phenotypes of PH, pathophysiology, therapeutic strategies, and ongoing challenges in this patient population.

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Introduction and Epidemiology

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and is frequently 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 modalities, with estimates ranging from 30-80%.[1] The hemodynamic and functional alterations that occur in the setting of abnormal cardiovascular structure and function contribute to the development of PH.[2] PH-HFpEF is associated with dyspnea, ventilatory impairments, reduction in aerobic capacity, high symptom burden, an increase in hospitalizations, and higher mortality.[3] The present paper on PH-HFpEF reviews the definition and classification, pathophysiology, challenges with diagnosis, and current and emerging treatment strategies.

Definition and Classification

The hemodynamic definition of pulmonary hypertension due to left heart disease (PH-LHD), also classified as World Health Organization (WHO) Group 2 PH, has been proposed during the 6th WSPH as a mPAP >20 mm Hg and a PAWP >15mmHg as measured by right heart catheterization (RHC).[4] The lower threshold of mPAP is based on reference data in healthier controls and was selected to harmonize with the new definition of PAH.[5] Among those with recognized PH-LHD, individuals are now stratified into IpcPH and CpcPH solely based on PVR of < or ≥ 3 Wood units (WU). CpcPH, is associated with reduced RV function and increased morbidity and mortality compared to IpcPH.[6] A recent analysis of 40,082 patients undergoing RHC in the U.S Veterans Affairs health-care system found excess adjusted all-cause mortality began at a threshold of 2.2 WU, suggesting even lower PVR values may be clinically relevant.[7] Finally, PAC, pulmonary arterial compliance (PAC), (estimated as stroke volume/PA pulse pressure), and pulmonary arterial elastance (Ea), defined as systolic PA pressure/stroke volume, are

both impacted by left atrial hypertension and PVR. They may better represent the total RV afterload compared to pre-capillary parameters. Although they are associated with more significant RV dysfunction and are better predictors of outcomes in PH-HFpEF, they are not helpful in distinguishing IpcPH and CpcPH.[8]

As these definitions and concepts rely heavily on hemodynamic definition, proper measurements of both pressures and cardiac output become essential. While directly measured cardiac output remains the gold standard measurement, the use of a metabolic cart for indirect calorimetry is not widespread in clinical practice. More often, indirect or 'assumed' Fick is utilized, though it has been demonstrated that its use may lead to inaccurate measures of cardiac output in the setting of heart failure and PH.[9,10] Therefore, thermodilution technique is preferred even in the setting of tricuspid regurgitation and low cardiac output.[11]

Pathophysiology

Pulmonary vasculature

In patients with HFpEF, abnormal myocardial active relaxation and increased passive stiffness of the left ventricle leads to elevation in left ventricular and thus left atrial pressures to maintain cardiac output.[12] Left atrial pathology itself may further contribute, exposing the lung vasculature to passive elevation in pressure.[13] Ultimately, elevated pressure and/or poor cardiac output leads to the development of a pre-capillary component due to pulmonary vasoconstriction, which is at least partially functional, and in some cases, structural remodeling of the pulmonary veins, capillaries, and arteries occur.[14,15]

Several factors contribute to the functional pathology in PH-HFpEF. Left atrial hypertension causes stress failure of the alveolar-capillary junction with the development of pulmonary edema. The edema activates inflammatory mediators that increases endothelin-1 expression, decrease in nitric oxide and natriuretic peptide activity. This may also 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 and colleagues, in a prospective hemodynamic study of 38 patients with HFpEF with 20 controls, found that the HFpEF subjects with PH displayed activation of endothelin and adrenomedullin neurohormonal pathways. The C-terminal pro-endothelin-1 and MR—pro ADM levels were strongly correlated with mean PA pressure ($r = 0.73$ and 0.65, both $P < 0.0001$) and PAWP ($r = 0.67$ and 0.62, both $P < 0.0001$) and inversely correlated with PAC ($r = -0.52$ and -0.43, both $P < 0.001$).[18] As mentioned above, left atrial hypertension also lowers PAC, making the vasculature stiff, increasing pulmonary pulse pressure, and indirectly increasing PVR. Furthermore, engorged lymphatics and edema may compress small distal lung arterioles, contributing to the pre-capillary component.[19]

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 PH-HFpEF, Fayyaz, et al found evidence of significant venous remodeling, with similar pathologic appearance to pulmonary veno-occlusive disease. In keeping, it was venous and intermediate vessel changes that were more closely associated with pulmonary pressures than the arterial remodeling.[20] Angiotensin II and transforming growth factor-beta 1, the most potent stimulators of collagen synthesis have, been implicated in the remodeling process.[21]

The development of functional vasoconstriction and remodeling are presumed to be pathologic, though it remains possible that these mechanisms are instead compensatory; that is, to "protect" the left heart from excessive preload. In a cohort free of cardiac disease, higher endothelin-1 levels at

baseline were protective of future heart failure events and were also associated with smaller LV size and higher LV ejection fraction.[22] Animal models of HFpEF and specifically PH-HFpEF have recently been developed, and may ultimately improve our understanding of the development of pulmonary vascular disease as well as heart dysfunction.[23,24]

Right Ventricle

The function of the right ventricle (RV) is likely the most important prognostic factor in PH-HFpEF.[25,26] RV diastolic dysfunction may occur early in the disease course. In a study of 24 compensated HFpEF patients with preserved CO and mildly elevated pulmonary pressures and 9 patients without heart failure symptoms who underwent RV pressure-volume measurement, increased RV stiffness and prolonged RV relaxation was present, though 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 are largely unknown. Co-morbidities like atrial fibrillation (AF) and obesity frequently co-exist in HFpEF patients and may contribute to the inflammatory milieu, right ventricular fibrosis, and even myocyte dysfunction. In 63 HFpEF patients with RV septal endomyocardial biopsy, those with marked obesity exhibited more depressed RV systolic sarcomere function yet less passive myocyte stiffening.[30] Thus, although not well characterized, it appears certain patient phenotypes may have an “at-risk” RV less able to compensate for increases in afterload.

RV-LV Interactions and Atrial Fibrillation

Ventricular interaction may play a significant role in the pathophysiology and functional limitations witnessed in PH-HFpEF, particularly in those with CpcPH.[31] LV transmural pressure, estimated as PAWP minus right atrial pressure (RAP), represents the true distending pressure of the LV (i.e. preload). In HFpEF without PH and IpcPH, PAWP typically increases out of proportion to RAP during exertion, increasing the LV transmural pressure. However, CpcPH patients demonstrate greater increases in RAP 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 has also been described in a sub-phenotype of HFpEF with permanent atrial fibrillation. Reduced left atrial compliance and impaired mechanics are associated with increasing burden of atrial fibrillation. Atrial fibrillation and left atrial dysfunction appear to be strong promotors of PH in HFpEF. [32]

Diagnosis of PH-HFpEF

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 PH-HFpEF, which can easily be misdiagnosed as PAH.[2] Factors associated with PH-LHD include the presence of AF, left atrial enlargement, age > 60 years, coronary artery disease, and BMI > 30 kg/m2 (TABLE 1), and these factors help determine the pre-test probability of PH-LHD. The physical exam and chest X-ray provide signs of fluid retention or signs of RV failure. Transthoracic echocardiography (TTE) serves as an excellent screening tool and is the first step in the evaluation of patients suspected of PH. While elevated PA systolic pressures (PASP) values derived from Doppler

echocardiography correlate with the presence of elevated pulmonary pressures, the accuracy of PASP 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 estimating pressures in the presence of an incomplete signal.[34] Pulmonary function testing can identify associated lung disease and aid in PH classification. Cardiopulmonary exercise testing (CPET) may be diagnostically useful as higher Ve/VCO2 slope is associated with more significant pre-capillary disease whereas the presence of exercise oscillatory ventilation (EOV) is more common in isolated heart failure.[35] Individuals with CpcPH should be ruled out for chronic thromboembolic disease and other conditions associated with pre-capillary disease as guided by history, physical exam and diagnostic evaluation.

Though TTE is the recommended screening tool, RHC remains the gold standard for diagnosis and proper phenotyping.[36] Most importantly, PAH must be excluded given the disparate therapeutic strategies between it and PH-HFpEF. The key hemodynamic differentiator is the PAWP, which is typically measured at end-expiration during normal respiration when intrathoracic pressure is closest to zero.[37] 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, though in these two populations proper measurement remains a point of debate.[38,39] Whenever the PAWP tracing morphology is atypical or pre-capillary PH is suspected clinically despite a measured PAWP >15 mm Hg, a PAWP oxyhemoglobin saturation content should be analyzed.[40] A truly wedged catheter will yield a oxyhemoglobin saturation reflective of the post-capillary pulmonary bed, typically >90-95%. 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-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 over-represented among men and women with mildly elevated mPAP (from 19-24mmHg).[41] As

such, particularly among individuals with mild PH, the pretest probability for PH-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 a diagnostic RHC be performed before volume status optimization.[11] When there is an intermediate to high probability of PH-LHD, but hemodynamics meet criteria for a pre-capillary disease, additional testing should be considered. FIGURE outlines a suggested algorithm from the 6th WSPH.[37] Given the practical and technical challenges with exercise, a fluid challenge is generally the preferred way to detect occult left heart disease, specifically when differentiating group 1 from group 2 PH. A PAWP >18 mm Hg immediately following the administration of 500 cc of normal saline over 5 minutes (or weight-based dosing of 7 cc/kg) is considered abnormal and suggestive of PH-LHD.[37,4243] At expert centers, cycle ergometry may be performed as an alternative, with a cutoff of PAWP ≥25 mmHg during supine exercise (or ≥20 mmHg during upright exercise) generally accepted as representing the presence of left heart disease. It should be noted, however, that pressures taken during exercise may vary significantly depending on how the PAWP is measured in respect to the respiratory cycle.[36]. The position statement from ERS recommends averaging over the respiratory cycle during exercise.[44] The multi-point slope of PAWP and cardiac output may prove to be a more reliable measure to discriminate between occult LHD and normal left-sided response to exercise, with > 2 mm Hg/L/min being considered abnormal.[45] It may also be less prone to issues with respiratory swings if all pressures are measured in a consistent manner.[46]

Therapeutic strategies

The significant gaps in understanding the complex pathobiology processes and comorbidities that complicate or drive the development and progression of PH has rendered the search for effective

therapies particularly difficult. Furthermore, PH may represent a marker of disease severity rather than an optimal target for therapy. Select clinical trials with biologic plausibility to treat PH-HFpEF are summarized in TABLE 2. Currently, there are no pharmacologic agents that are approved to specifically 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 co-morbidities are the mainstays of therapy in HFpEF, and therefore, PH-HFpEF. In addition to normalization of intracardiac and pulmonary pressures and symptom relief, diuresis associated 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 CHAMPION trial was a prospective randomized control trial that enrolled 550 patients with heart failure with both reduced and preserved ejection fraction. Subjects randomized to hemodynamic guided care had substantially more medication titrations (principally diuretics) and experienced a significant reduction in heart failure hospitalizations compared to controls. For one of the first times, subjects with HFpEF and HFrEF showed similar benefit.[47] Post-marketing surveillance study of more than 2000 patients (34% PH-HFpEF) yielded similar results.[48]

The role of mineralocorticoid receptor antagonist spironolactone in HFpEF was studied in the TOPCAT trial.[49] Although the trial failed to meet its primary endpoint, perhaps due to enrollment irregularities in Russia and Georgia, a reduction in HF hospitalizations were noted.[50] 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.[51] Whether this may add particular benefit in PH-HFpEF is unknown. In addition, a large cohort of veterans with pulmonary hypertension suggested a mortality benefit with ace inhibitors and angiotensin-receptor blockade. This included veterans with left heart disease; however, HFpEF was not specifically differentiated in this cohort.[52]

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 prognostically relevant and may be associated with unique and targetable phenotypes.[53,54] The presence of underlying valvular heart disease should be investigated and considered as potential therapeutic targets. 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, though data from a prospective, randomized control trial is needed.[55] With the increasing prevalence of an obesity/metabolic HFpEF phenotype, weight loss management, and aerobic exercise are critical interventions and have both been shown to improve exercise tolerance and reduce body weight in HFpEF.[56]

PAH targeted therapies

Studies of pulmonary vasodilators in PH-HFpEF have largely been disappointing. Although phosphodiesterase-5 (PDE5) inhibitors have proven efficacious in PAH, their role in PH-HFpEF remains unproven. In a prospective placebo-controlled single-center trial of 44 patients with PH-HFpEF defined by elevated pulmonary artery systolic pressure of (PASP) > 40 mm Hg and severe right ventricular dysfunction, sildenafil use compared to placebo showed improvement in pulmonary pressures, RV function and RV dimensions at 6 months.[57] Though it was not enriched for CpcPH, the RELAX study of sildenafil use in subjects with HFpEF did not improve mean pulmonary artery pressure, PAWP, CO, exercise tolerance or VO2.[58,59] In a post hoc analysis of the trial, sildenafil failed to reduce RV afterload.[60] Similar results were obtained in other studies of predominately IpcPH.[58] In a randomized double-blind placebo-controlled trial of 222 patients (108 CpcPH and 80 IpcPH) with PH-HFpEF related to successfully corrected (at least 1 year before enrollment) valvular heart disease, sildenafil treatment

was associated with worse clinical outcomes compared to placebo.[61] The PASSION trial evaluating the effects of tadalafil on HFpEF and CpcPH is currently underway.

While PDE5 inhibitors have failed to show benefit in undifferentiated PH-HFpEF and remain under investigation in CpcPH, another class of medications affecting the same downstream signaling pathways has also been evaluated. Whereas PDE5 inhibitors prevent the breakdown of cGMP – a vasodilatory and antiproliferative molecular signal – the soluble guanylyl cyclase stimulators (sGC stimulators) function to directly increase sGC levels in the vasculature and other tissues. DILATE-1 trial evaluated the role of the sGC stimulator riociguat compared to placebo in 39 patients with PH-HFpEF and notably included 5 patients with CpcPH. No significant change in mPAP or PVR at 6 hours was noted in this proof-of-concept study. Subsequent, large prospective randomized trials of sGC-stimulators have shown no benefit in enrolled, undifferentiated HFpEF subjects.[62-64] Finally, several investigations targeting the endothelin pathway have been reported. A study of the selective endothelin type A (ET_A) receptor sitaxsentan in 192 HFpEF subjects did not meet statistical significance for end points including New York Heart Association (NYHA) functional class, heart failure hospitalizations, measures of diastolic function, or quality of life questionnaire scores. However, there was a significant increase in median treadmill time.[65] The MELODY-1 evaluated the acute role of the endothelin receptor antagonist macitentan in patients with CpcPH identified by diastolic pressure gradient ≥7 mmHg and PVR ≥ 3WU. The trial was powered to evaluate safety endpoints. At 12 weeks, more adverse events were noted with macitentan compared to placebo with no improvement in PVR or mean right atrial pressure.[66] Unfortunately, the SERENADE trial, which specifically enrolled patients with HFpEF and pulmonary vascular disease or RV dysfunction was stopped prematurely (NCT03153111). **At present, PAH-specific therapies should be avoided in PH-HFpEF**.[37] This recognition is relevant given relatively recent real-world evidence suggesting that PAH specific therapies may be prescribed nearly as frequently for PH-LHD as PAH and

are used more frequently than might be assumed for PH-LHD in the rare setting of complex and multifactorial etiologies.[67]

Early phase or investigational therapies

Several on-going pharmacologic and device therapies are being studied in PH-HFpEF. Early phase studies of intra-atrial septal devices (IASD) have shown promise in exercise-induced HFpEF but have not specifically enrolled patients with PH-HFpEF.[68,69] In early studies, IASD were associated with reduction in PVR, pulmonary Ea and improvement in PAC at 6 months.[69] In an open-label study, the use of IASD was associated with sustained improvements in NYHA functional class ($P < 0.001$), quality of life ($P < 0.001$) and 6- minute walk distance ($P < 0.01$).[70] Whether those with CpcPH may be at higher risk of RV dilation or dysfunction after these therapies remain unknown. In a study of 37 patients with group 2 PH with HF with EF of at least 40%, NYHA II or III heart failure, once weekly Levosimendan compared to placebo showed did not significantly reduce the primary endpoint of exercise PAWP (-1.4 mmHg, 95% CI [-7.8, 4.8],p=0.65). However, Levosimendan reduced PAWP measured across all exercise stages (-3.9±2.0 mmHg, p=0.047), and resulted in a 29.3 meter (95% CI [2.5, 56.1], p=0.033) improvement in 6 minute walk distance compared to placebo.[71] Metformin is currently being studied in a phase II trial for PH-HFpEF (NCT03629340) based upon 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.[72] In keeping with the metabolic mechanisms contributing to HFpEF, two large, randomized trials (EMPEROR-Preserved - NCT03057951; DELIVER - NCT03619213) are evaluating the role of SGLT2 inhibitors in HFpEF; results of which could inform the management of PH-HFpEF.

Nitrite, which is reduced to nitric oxide by hemoglobin, is currently being studied in an oral formulation for PH-HFpEF (NCT03015402), having shown promise in an inhaled formulation in PH-HFpEF predominately through improvement in PAC. However, a broader study in HFpEF (uncontrolled for PH) did not show improvement in exercise capacity as assessed by CPET and 6-minute walk distance.[73] Early-phase studies of oral milrinone have also been conducted suggesting improvement in exercise hemodynamics and improved quality of life measures.[74] Finally, PA denervation therapy in CpcPH was studied in the PADN-5 study, which included approximately 40% of subjects with HFpEF. Compared with sildenafil alone, PA denervation resulted in a significant increase in 6-min walk and lower PVR.[75] Additional studies of this potentially promising therapy, such as TROPHY-II (NCT03611270) are underway.

Conclusion

In HFpEF, the development of pulmonary hypertension 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 have largely been disappointing but novel therapeutic strategies are currently being studied.

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Figure Legend

Figure. Hemodynamic assessment of pulmonary hypertension (PH) due to heart failure with preserved ejection fraction (HFpEF). RV: right ventricular; RHC: right heart catheterization; LHD: left heart disease; PAWP: pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure; CTEPH: chronic thromboembolic PH. a) Pre-test probability of PH-LHD is based on the features presented in table 1. RHC is recommended in intermediate probability when risk factors of pulmonary arterial hypertension/CTEPH are present and/or if there is evidence of right ventricle abnormality. 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/high probability (table 1) and PAWP between 13 and 15 mmHg, PH-HFpEF is not excluded; provocative testing (tables 2 and 3) should be considered. [#]: for patients with systemic sclerosis, risk factors for CTEPH and/or unexplained dyspnea; [¶]: after [2]; [+]: if PAWP >15 mmHg, LVEDP validation should be considered. Reproduced with permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801897; **DOI:** 10.1183/13993003.01897-2018 Published 24 January 2019.[41]

Abbreviation List

HFpEF: heart failure with preserved ejection Fraction

PH: pulmonary hypertension

IpcPH: isolated post-capillary pulmonary hypertension

CpcPH: combined post- and pre-capillary pulmonary hypertension

WSPH: World Symposium on Pulmonary Hypertension

PAH: Pulmonary Arterial Hypertension

mPAP: mean pulmonary artery pressure

LHD: left heart disease

PAWP: pulmonary artery wedge pressure

CO: cardiac output

WU: Wood units

RHC: right heart catheterization

PVR: pulmonary vascular resistance

PAC: pulmonary arterial compliance

Ea: pulmonary arterial elastance

RV: right ventricular

BMI: body mass index

TTE: transthoracic echocardiogram

PASP: pulmonary artery systolic pressure

AF: atrial fibrillation

PDE5: phosphodiesterase-5

sGC: soluble guanylyl cyclase

CPET: Cardiopulmonary Exercise Test

Table 1. Pre-test probability of left heart disease (LHD) phenotype versus Pulmonary arterial hypertension or pre-capillary PH

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidemia, glucose intolerance/diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention[#]	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*/*e*′ <13
CPET	Mildly elevated V'_E/V'_{CO2} slope; EOV	Elevated V'_E/V'_{CO2} slope *or* EOV	High V'_E/V'_{CO2} slope; no EOV
Cardiac MRI	LA strain or LA/RA >1		No left heart abnormalities

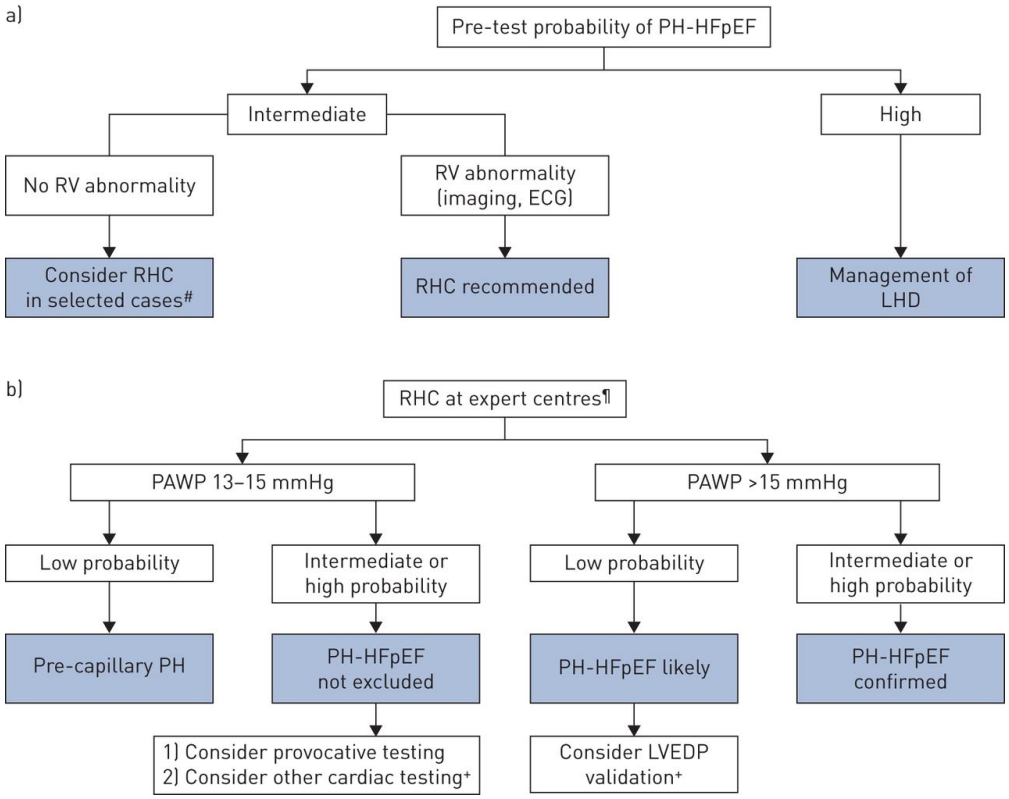
LBBB: left bundle branch block; LVH: left ventricular hypertrophy; RV: right ventricular; LA: left atrial; *E*/*e*′: early mitral inflow velocity/mitral annular early diastolic velocity ratio; CPET: cardiopulmonary exercise testing; V'_E: minute ventilation; V'_{CO2}: carbon dioxide production; EOV: exercise oscillatory ventilation; MRI: magnetic resonance imaging; RA: right atrial. [#]: coronary artery and/or valvular surgical and/or non-surgical procedures, including percutaneous interventions. Reproduced with permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801897; **DOI:** 10.1183/13993003.01897-2018 Published 24 January 2019.[41]

Table 2: Representative Clinical Trials of Pulmonary Hypertension in Heart Failure with Preserved Ejection fraction

Trial	Intervention	Sample Size & Duration	Inclusion Criteria	Study Design	Endpoints	Results
Guazzi M et al *Circulation 2011*	Sildenafil vs. placebo	N=44; 6 and 12 months	LVEF ≥50%, sinus rhythm, PASP ≥40mmHg	Prospective, double-blind, randomized, single-center	Hemodynamics and RV function on echo	Sildenafil: Reductions in mPAP, PVR, RAP, and PAWP with improvements in TAPSE and QOL.
Redfield et al *JAMA 2013* (**RELAX-HF**)	Sildenafil vs. placebo	N = 216, 24 weeks	- pVO_2 <60% normal - NT-proBNP >400 pg/mL or NT-proBNP <400 with mPCWP >20 mmHg	Prospective, randomized, multi-center, double-blind, placebo-controlled	Change in pVO_2 after 24 weeks (*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=0.90*) at 24 weeks
Abraham et al *Circ HF 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 months	- NYHA class III, HF hospitalization in previous 12 months	Prospective, randomized, multi-center, single-blind (post-hoc analysis)	Rate of HF hospitalizations after 6 months	Incidence rate ratio for heart failure hospitalization after 6 months 0.54 for LVEF >40% in treatment vs. control (*P<0.0001*)
Bonderman et al *CHEST 2014* (**DILATE-1)**	Riociguat vs. placebo	N = 477, 6 hours	- LVEF >50%, mPAP ≥25 mmHg, PAWP > 15 mmHg (at rest)	Prospective, randomized, multi-center, double-blind, placebo-controlled	Peak decrease in mPAP, change in stroke volume, RV end-diastolic area	Riociguat: peak decrease in mPAP 10 mmHg vs 11 mHg with placebo (*p=0.6*); +9 mL in stroke volume over placebo (P=0.04)
Redfield el al *NEJM 2015* (**NEAT- HFpEF**)	Isosorbide mononitrate vs. placebo (6-week dose-escalation regimen of isosorbide mononitrate with subsequent crossover to the other group for 6 weeks).	N=110; 12 weeks	LVEF ≥50% and objective evidence of heart failure,	Prospective, multi-center, 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
Borlaug et al *JACC 2015*	Intravenous sodium nitrite vs. placebo compared via invasive hemodynamics and measured gas	N=28; 15 minutes after drug administration	LVEF ≥50% and symptoms of HF, PAWP >15 mmHg at rest or ≥25 mmHg with exercise	Prospective, single-center, double-blind, placebo-controlled, parallel-group	Exercise PAWP, mean PAP, mPAP/CO ratio, LVSW Sodium nitrite infusion acutely	Intravenous inorganic nitrite led to acute attenuation of PAWP rise with exercise, reduction in exercise-induced PH, and improved CO reserve.

	exchange 15 min. after administration					
Simon et al *JCI Insight 2016*	Aerosolized sodium nitrite	N=36; 15-60 minutes	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	Baseline hemodynamics prior to and following inhaled NO as well as at 15, minute intervals following 45mg and then 90mg aerosolized sodium nitrite	Aerosolized sodium nitrite was well-tolerated, and in PH-HFpEF (n=10). Compared with other PH groups, PH-HFpEF subjects experienced greatest decrease in PCWP, RAP, RV, and PAP. Pulmonary artery compliance also improved in PH-HFpEF subjects.
Borlaug et al *Circ Res 2016*	Nebulized inhaled sodium nitrite 90mg vs placebo	N=26; hemodynamics at rest, then after 5 minutes of exercise, then 5 minutes after intervention	HFpEF (LVEF ≥50%, PCWP at rest >15 mmHg or with exercise ≥25 mmHg)	Prospective, randomized, single-center, double-blind, placebo-controlled, parallel-group	Primary end point: PCWP during exercise; Secondary end points included changes in PCWP and other hemodynamic measurements	Nebulized inhaled nitrite reduced biventricular pressures and PAPs at rest and during exercise
Vachiéry et al *Eur Respir J 2017* (**MELODY-1**)	Macitentan vs. placebo	N = 63, median treatment duration of 12 vs 12.1 weeks in macitentan vs. placebo groups	- LVEF ≥ vs. < 50% (stratified by LVEF) and CpcPH confirmed by RHC with mPAP >25 mmHg, PAWP >15 mmHg, and < 25 mmHg, and PVR at rest ≥3 WU with DPG ≥7 mmHg	Prospective, randomized, multi-center, double-blind, placebo-controlled	Composite primary endpoint 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 non-significant but numerically greater number of adverse events and serious adverse events with macitentan vs. placebo.
Pieske et al *Eur Heart J 2017* (**SOCRATES-PRESERVED**)	Vericiguat vs. placebo	N=477, 12 weeks	- LVEF > 45%	Prospective, randomized, double-blind, placebo-controlled dose-finding study	Change from baseline NT-proBNP and left atrial volume at 12 weeks	Vericiguat: no significant change in NT-proBNP or LAV at 12 weeks vs. placebo, associated with improved QOL
Reddy et al *Circ Res 2019*	Inhaled Albuterol vs. placebo	N=30, single episode of invasive	LVEF ≥ 50%, resting end-expiratory	Prospective, randomized, double-blind,	Exercise PVR, Resting PVR, rest and	Albuterol: reduction in exercise PVR -0.6 ± 0.5 vs. +0.1 ± 0.7 WU (*p=0.003*).

(**Albuterol in HFpEF**)		hemodynamic exercise-testing	PCWP ≥15 or exercise PCWP ≥ 25 mmHg at 20 W workload	parallel-group, placebo-controlled trial	exercise PCWP, other measures of RV reserve	Albuterol also improved PA compliance, arterial elastance, RV-PA coupling, and cardiac output
Armstrong et al *JAMA 2020* (**VITALITY-HFpEF**)	Vericiguat, up-titrated 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 weeks	LVEF ≥ 45%, NYHA class II-III, within 6 months of a recent decompensation, and elevated natriuretic peptides	Phase 2b randomized, double-blind, placebo-controlled, multicenter trial	Physical limitation score (PLS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ).	Vericiguat: No improvement of PLS of KCCQ compared with placebo; no change in 6-minute walk distance
Udelson et al *JAMA 2020* (**CAPACITY-HFpEF**)	40 mg of praliciguat daily or placebo	N=196, 12 weeks	LVEF ≥ 40%, impaired peak $V'O_2$, and at least 2 conditions associated with NO deficiency	Randomized, double-blind, placebo-controlled, phase 2 trial.	Change from baseline in peak $V'O_2$ in patients who completed at least 8 weeks of assigned dosing	Praliciguat: No difference in peak $V'O_2$ or 6-minute walk distance



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

Chakradhari Inampudi M.D.[1](Inampudi@musc.edu), Daniel Silverman M.D[1] (Silvermd@musc.edu), Marc A. Simon M.D, M.S.[2] (Marc.Simon@ucsf.edu), Peter J. Leary M.D., Ph.D.[3](Learyp@uw.edu), Kavita Sharma, M.D.[4](Ksharma8@jhmi.edu), Brian A. Houston M.D[1](houstobr@musc.edu), Jean-Luc Vachiery M.D.[5](Jeanluc.vachiery@erasme.ulb.ac.be), Francois Haddad M.D.[6](Fhaddad@stanford.edu), Ryan J Tedford, M.D[1](TedfordR@musc.edu)

1. Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC USA
2. Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, CA USA
3. Department of Medicine, University of Washington, Seattle, Washington USA
4. Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD USA
5. Département de Cardiologie Cliniques Universitaires de Bruxelles-Hôpital Erasme, Brussels, Belgium.
6. Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford CA USA

First Author:

Chakradhari Inampudi M.D.
Assistant Professor Medicine
30 Courtenay Drive, MSC592
Charleston, SC 29425, USA
Email: Inampudi@musc.edu
Twitter Handle: @chakri0012

Correspondence to:

Ryan J. Tedford, MD, FACC, FAHA, FHFSA
Dr. Peter C. Gazes Endowed Chair in Heart Failure
Professor of Medicine/Cardiology

Chief, Heart Failure
Medical Director, Cardiac Transplantation
Director, Advanced Heart Failure & Transplant Fellowship Training Program
Medical University of South Carolina (MUSC)
30 Courtenay Drive
BM215, MSC592
Charleston, SC 29425
(843) 792-3355 *office*
(843) 876-4990 *fax*
Email: TedfordR@musc.edu
Twitter Handle: @RyanTedfordMD

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Key Words/Terms: Heart failure with Preserved Ejection Fraction, Pulmonary Hypertension, Right Ventricle; Diastolic Heart Failure; Left Heart Disease

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and is frequently associated with pulmonary hypertension (PH). PH-HFpEF may be difficult to distinguish from pre-capillary forms of PH, though this distinction is crucial as therapeutic pathways are divergent for the two conditions. A comprehensive and systematic approach utilizing history, clinical exam, non-invasive and invasive evaluation with and without provocative testing may be necessary for accurate diagnosis and phenotyping. Once diagnosed, PH-HFpEF can be subdivided into isolated post-capillary pulmonary hypertension (IpcPH) and combined post- and pre-capillary pulmonary hypertension (CpcPH) based on the presence or absence of elevated pulmonary vascular resistance (PVR). 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 pulmonary hypertension for PH-HFpEF remain limited. In this review, we aim to provide an updated overview on clinical definitions and hemodynamically characterized phenotypes of PH, pathophysiology, therapeutic strategies, and ongoing challenges in this patient population.

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Introduction and Epidemiology

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure and is frequently 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 modalities, with some estimates ranging from 30-80%.[1] The hemodynamic and functional alterations that occur in the setting of abnormal cardiovascular structure and function contribute to the development of PH.[2] PH-HFpEF is associated with dyspnea, ventilatory impairments, reduction in aerobic capacity, high symptom burden, an increase in hospitalizations, and higher mortality.[3] The present paper on PH-HFpEF reviews the definition and classification, pathophysiology, challenges with diagnosis, and current and emerging treatment strategies.

Definition and Classification

~~Since the initial description of PH in 1940, the novel mechanistic insights by Paul Wood from 1956-1958, and the first version of clinical classification in 1973, the diagnosis has gone through a series of iterative changes. Based partially on expert opinion and to minimize the chances of overdiagnosis of pulmonary arterial hypertension (PAH), a mean pulmonary artery pressure (mPAP) of ≥ 25mmHg was first used to define PH. At the proceedings of the fourth World Symposium of Pulmonary Hypertension (WSPH), PH due to left heart disease (LHD) was divided into passive versus reactive or "out-of-proportion" PH based on the transpulmonary gradient (TPG): calculated as mean pulmonary artery pressure (mPAP) minus pulmonary arterial wedge pressure (PAWP). A TPG > 12mmHg was recommended as a marker indicative of pulmonary vascular remodeling and was commonly used to distinguish passive from reactive PH; however, the specificity of this approach was later questioned as the gradient may be influenced by changes in cardiac output (CO), recruitment and distension of~~

~~pulmonary vessels, and loading conditions. In 2013, the diastolic pressure gradient (DPG; diastolic pulmonary artery pressure minus PAWP) was proposed to distinguish isolated post-capillary PH (IpcPH) from combined post- and pre-capillary (CpcPH). The DPG may be less influenced by flow and loading conditions, and a DPG < 7 mmHg defined IpcPH whereas ≥ 7 mmHg defined CpcPH; however, due to concerns related to measurement fidelity and mixed reports on its prognostic utility, DPG also fell out of favor. This has been reflected in the last international guidelines on PH, in which CpcPH was defined as DPG > 7 mm Hg and/or PVR > 3 WU.~~

The hemodynamic definition of pulmonary hypertension due to left heart disease (PH-LHD), also classified as World Health Organization (WHO) Group 2 PH, has been proposed during the 6th WSPH as a mPAP > 20 mm Hg and a PAWP > 15mmHg as measured by right heart catheterization (RHC).[4] The lower threshold of mPAP is based on reference datae in healthier controls and was selected to harmonize with the new definition of PAH.[5] ~~As these definitions and concepts rely heavily on hemodynamic definition, proper measurements of cardiac output and pulmonary pressures become essential. While directly measured Fick, cardiac output remains the gold standard measurement, the use of a metabolic cart for indirect calorimetry is not widespread in clinical practice. More often, indirect or 'assumed' Fick is utilized, though it has been demonstrated that its Wolf et al. and others have demonstrated that use of the assumed Fick may lead to inaccurate measures of cardiac output and so the thermodilution technique is preferred even in the setting of tricuspid regurgitation and low cardiac output~~ Among those with recognized PH-LHD, individuals are now stratified into IpcPH and CpcPH solely based on ~~pulmonary vascular resistance (~~PVR~~), defined as TPG/CO,~~ of < or ≥ 3 Wood units (WU). CpcPH, ~~defined by PVR,~~ is associated with reduced RV function and increased morbidity and mortality compared to IpcPH.[6] A recent analysis of 40,082 patients undergoing RHC in the U.S Veterans Affairs health-care system found excess adjusted all-cause mortality began at a threshold of 2.2 WU, suggesting even lower PVR values may be clinically relevant.[7] Finally, PAC, pulmonary arterial compliance (PAC), (estimated as

stroke volume/PA pulse pressure), and pulmonary arterial elastance (Ea), defined as systolic PA pressure/stroke volume, are both impacted by left atrial hypertension and PVR. They may better represent the total RV afterload compared to pre-capillary parameters. Although they are associated with more significant RV dysfunction and are better predictors of outcomes in PH-HFpEF, they are not helpful in distinguishing IpcPH and CpcPH.[8]

As these definitions and concepts rely heavily on hemodynamic definition, proper measurements of both pressures and cardiac output become essential. While directly measured cardiac output remains the gold standard measurement, the use of a metabolic cart for indirect calorimetry is not widespread in clinical practice. More often, indirect or 'assumed' Fick is utilized, though it has been demonstrated that its use may lead to inaccurate measures of cardiac output in the setting of heart failure and PH.[9,10] Therefore, thermodilution technique is preferred even in the setting of tricuspid regurgitation and low cardiac output.[11]

~~Pulmonary arterial compliance (PAC) (estimated as stroke volume/PA pulse pressure), a global parameter of pulmonary artery distensibility, and pulmonary arterial elastance (Ea), defined as systolic PA pressure/stroke volume, may better represent the total RV afterload compared to pre-capillary parameters. Although they are associated with more significant RV dysfunction and are better predictors of outcomes in PH-HFpEF, they are not helpful in distinguishing IpcPH and CpcPH.~~

Pathophysiology

Pulmonary vasculature

In patients with HFpEF, abnormal myocardial active relaxation and increased passive stiffness of the left ventricle leads to elevation in left ventricular and thus left atrial pressures to maintain cardiac

output.[12] Left atrial pathology itself may further contribute, exposing the lung vasculature to passive elevation in pressure.[13] Ultimately, elevated pressure and/or poor cardiac output leads to the development of a pre-capillary component due to pulmonary vasoconstriction, which is at least partially functional, and in some cases, structural remodeling of the pulmonary veins, capillaries, and arteries occur.[14,15]

Several factors contribute to the functional pathology in PH-HFpEF. Left atrial hypertension causes stress failure of the alveolar-capillary junction with the development of pulmonary edema. ~~and impairment of gas exchange, contributing to dyspnea, hypoxemia, and vasoconstriction.~~ The edema activates inflammatory mediators that increases endothelin-1 expression, decrease in nitric oxide and natriuretic peptide activity. This may also ~~,~~ lead~~ing~~ 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] ~~Overproduction of endothelin-1, decreased nitric oxide bioavailability, activation of the renin-angiotensin-aldosterone system and neurogenic activation lead to endothelial dysfunction.~~ Obokata and colleagues, in a prospective hemodynamic study of 38 patients with HFpEF with 20 controls, found that the HFpEF subjects with PH displayed activation of endothelin and adrenomedullin neurohormonal pathways. The C-terminal pro-endothelin-1 and MR—pro ADM levels were strongly correlated with mean PA pressure (r = 0.73 and 0.65, both P < 0.0001) and PAWP (r = 0.67 and 0.62, both P < 0.0001) and inversely correlated with PAC (r = -0.52 and -0.43, both P < 0.001).[18] As mentioned above, left atrial hypertension also lowers PAC, making the vasculature stiff, increasing pulmonary pulse pressure, and indirectly increasing PVR. Furthermore, ~~Paul Wood even suggested that~~ engorged lymphatics and edema may~~can~~ compress small distal lung arterioles, ~~increasing PVR~~contributing to the pre-capillary component.[19] ~~Atrial fibrillation is closely associated with PH-HFpEF, whether as a cause for the left atrial remodeling that leads to left atrial hypertension, or as the effect. Finally, PAC, pulmonary arterial compliance (PAC), (estimated as stroke volume/PA pulse pressure),~~

impacted directly by left atrial hypertension. and pulmonary arterial elastance (Ea), defined as systolic PA pressure/stroke volume, may better represent the total RV afterload compared to pre-capillary parameters. Although they are associated with more significant RV dysfunction and are better predictors of outcomes in PH-HFpEF, they are not helpful in distinguishingwhich determines the blood storage capacity of the pulmonary circulation, is also impacted directly by left atrial hypertension. In healthy individuals, the principal determinant of compliance is PVR, and thus, a linear relationship exists between pulmonary artery systolic, mean, and diastolic pressures. However, as pressure is transmitted backward from the left heart, compliance declines for any given resistance. As compliance declines, pulmonary pulse pressure and mPAP increase due to a rise in systolic pulmonary artery pressure relative to diastolic pressure, further contributing to IpcPH and CpcPH. the pre-capillary component.

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 PH-HFpEFLHD, Fayyaz, et alPadang R et al found evidence of significant venous remodeling, with similar pathologic appearance to pulmonary veno-occlusive disease. In keeping, it was venous and intermediate vessel changes that were venous medial hypertrophy was the most common pathologic finding and correlated more closely associated with with higher pulmonary pressures than the arterial remodeling.[20] [20] The Pulmonary artery systolic pressure more correlated with venous or small indeterminate vessels percent intimal thickness. In 30 PH-HF who underwent RHC, numerically stronger association noted between transpulmonary gradient (TPG) and pulmonary vascular remodeling. Additionally, the venous and small vessel intimal thickening was noted to be more severe than arterial intimal thickening in PH-HFpEF. In the spectrum of PH-HFpEF, a subset of patients exhibits a unique phenotype that shares biological overlap with PAH. When evaluated at the cellular level, the pathways involved in lung microvasculature remodeling have also been shown to contribute to left atrial fibrosis. The new cell lines 'aerocyte' and 'general' capillary (gCap), as their roles

~~emerge may transform our understanding of their role in PH-HFpEF.~~ Angiotensin II and transforming growth factor-beta 1, the most potent stimulators of collagen synthesis have, been implicated in the remodeling process.[21] ~~In a swine model of isolated post-capillary pulmonary hypertension, pulmonary vein banding (n= 7) compared to Sham (n= 6) for 10 weeks resulted in upregulation of the endothelin pathway contributing to pre-capillary aspects in the initially isolated post-capillary pulmonary hypertension.~~

The development of functional vasoconstriction and remodeling are presumed to be pathologic, though it remains possible that these mechanisms are instead compensatory; that is, to ~~reduce blood return to the diseased left heart and~~ "protect" the~~optimize~~ left heart from excessive preload. In a cohort free of cardiac disease, higher endothelin-1 levels at baseline were protective of future heart failure events and were also associated with smaller LV size and higher LV ejection fraction.[22] Animal models of HFpEF and specifically PH-HFpEF have recently been developed, and may ultimately improve our understanding of the development of pulmonary vascular disease as well as heart dysfunction.[23,24]

Right Ventricle

The function of the right ventricle (RV) is likely the most important prognostic factor in PH-HFpEF.[25,26] RV diastolic dysfunction may occur early in the disease course. In a study of 24 compensated HFpEF patients with preserved CO and mildly elevated pulmonary pressures and 9 patients without heart failure symptoms who underwent RV pressure-volume measurement, increased RV stiffness and prolonged RV relaxation was present, though 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 are largely unknown. Co-morbidities like atrial fibrillation (AF) and obesity frequently co-exist in HFpEF patients and may contribute to the inflammatory milieu, right ventricular fibrosis, and even myocyte dysfunction. In ~~a representative sample of~~ 63 HFpEF patients with RV septal endomyocardial biopsy, those with marked obesity exhibited more depressed RV systolic sarcomere function yet less passive myocyte stiffening.[30] Thus, although not well characterized, it appears certain patient phenotypes may have an "at-risk" RV less able to compensate for increases in afterload.

RV-LV Interactions and Atrial Fibrillation

~~In addition to the abnormalities in RV function noted above,~~ vVentricular interaction may ~~also be seen~~play a significant role in the pathophysiology and functional limitations witnessed in PH-HFpEF, particularly in those with CpcPH. ~~In particular, distinct phenotypes IpcPH vs. CpcPH may be elucidated with exercise.~~[31] LV transmural pressure, estimated as PAWP minus right atrial pressure (RAP), represents the true distending pressure of the LV (i.e. preload). In HFpEF without PH and IpcPH, PAWP typically increases out of proportion to RAP during exertion, increasing the LV transmural pressure. However, CpcPH patients demonstrate greater increases in RAP 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.~~While left heart congestion appeared to drive increases in LV transmural filling pressures in patients with HFpEF without PH and in IpcPH, in CpcPH-HFpEF, left heart underfilling from increased RAP and increased RAP/PCWP ratio leads to reduced LV transmural filling pressure characterizing RV-LV interactions. Furthermore, left heart underfilling appeared to correlate directly~~

~~with the severity of pulmonary vascular disease present.~~ [31] Worsening pulmonary vascular disease, right heart failure and pericardial restraint has also been described in a sub-phenotype of HFpEF with permanent atrial fibrillation. Reduced left atrial compliance and impaired mechanics are associated with increasing burden of atrial fibrillation. Atrial fibrillation and left atrial dysfunction appear to be strong promotors of PH in HFpEF. [32]

Diagnosis of PH-HFpEF

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 PH-HFpEF, which can easily be misdiagnosed as PAH.[2] Factors associated with PH-LHD include the presence of AF, left atrial enlargement, age > 60 years, coronary artery disease, and BMI > 30 kg/m2 (TABLE 1), and these factors help determine the pre-test probability of PH-LHD. The physical exam and chest X-ray provide signs of fluid retention or signs of RV failure. Transthoracic echocardiography (TTE) serves as an excellent screening tool and is the first step in the evaluation of patients suspected of PH. ~~TTE has been shown to have moderate precision for identifying PH and determining severity.~~ While elevated PA systolic pressures (PASP) values derived from Doppler echocardiography correlate with the presence of elevated pulmonary pressures, the accuracy of PASP 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 estimating pressures in the presence of an incomplete signal.[34] Pulmonary function testing can identify associated lung disease and aid in PH classification. Cardiopulmonary exercise testing (CPET) may be diagnostically useful as ~~identify WHO Group 3 PH~~, higher Ve/VCO2 slope ~~cardiopulmonary exercise testing~~ is associated with more significant pre-capillary disease whereas the presence of exercise oscillatory ventilation (EOV) is more common in isolated heart failure.[35] ~~can provide data on VE/VCo2 slope that has been correlate with outcome in CPcPH, and cardiac magnetic resonance imaging can also aid in diagnosis in selected patients.~~ Individuals with CpcPH should be ruled out for chronic thromboembolic disease and other conditions associated with pre-capillary disease as guided by history, physical exam and diagnostic evaluation.

Though TTE~~echocardiography~~ is the recommended screening tool, RHC remains the gold standard for diagnosis and proper phenotyping.[36] Most importantly, PAH must be excluded given the disparate therapeutic strategies between it and PH-HFpEF. The key hemodynamic differentiator is the PAWP, which is typically measured at end-expiration during normal ~~tidal~~ respiration when intrathoracic pressure is closest to zero.[37] 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, though in these two populations proper measurement remains a point of debate.[38,39] Whenever the PAWP tracing morphology is atypical or pre-capillary PH is suspected clinically despite a measured PAWP >15 mm Hg, a PAWP oxyhemoglobin saturation content should be analyzed.[40] A truly wedged catheter will yield a oxyhemoglobin saturation reflective of the post-capillary 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-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 over-represented among men and women with mildly elevated mPAP (from 19~~–~~24mmHg).[41] As such, particularly among individuals with mild PH ~~pulmonary hypertension~~, the pretest probability for PH-LHD should be higher ~~under the new definition~~. 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 a diagnostic RHC be performed before volume status optimization.[11] When there is an intermediate to high probability of PH-LHD, but hemodynamics meet criteria for a pre-capillary disease, additional testing should be considered. FIGURE outlines a suggested algorithm from the 6th WSPH.[37] Given the practical and technical challenges with exercise, a fluid challenge is generally the preferred way to detect occult left heart disease, specifically when differentiating group 1 from

group 2 PH ~~at rest in this situation~~. A PAWP > 18 mm Hg immediately following the administration of 500 cc of normal saline over 5 minutes (or ~~in some cases using a~~ weight-based dosing of ~~(~~7 cc/kg) is considered abnormal and suggestive of PH-LHD.[37,4243] At expert centers, ~~upright or supine~~ cycle ergometry may be performed as an alternative, with a cutoff of PAWP ≥ 25 mm Hg during supine exercise (or ≥20 mmHg during upright exercise) generally accepted as representing the presence of left heart disease. It should be noted, however, that pressures taken during exercise may vary significantly ~~based on whether measurement is performed at end-expiration, or during the course of the respiratory cycle as advised in the 2015 ESC/ERS guidelines~~ depending on how the PAWP is measured in respect to the respiratory cycle.[36]. The position statement from ~~the 2015 ESC/~~ERS recommends averaging over the respiratory cycle during exercise.[44] ~~Although various cutoffs have been proposed for an abnormal PAWP during exercise,~~ Tthe multi-point slope of PAWP and cardiac output may prove to be a more reliable measure to discriminate between occult LHD and normal left-sided response to exercise, with > 2 mm Hg/L/min being considered abnormal.[45] ~~the best discriminator of occult LHD, with > 2 mm Hg/L/min being considered abnormal.~~ It may also be less prone to issues with respiratory swings if all pressures are measured in a consistent manner.[46]

Therapeutic strategies

The significant gaps in understanding the complex pathobiology processes and comorbidities that complicate or drive the development and progression of PH has rendered the search for effective therapies particularly difficult. Furthermore, PH may represent a marker of disease severity rather than an optimal target for therapy. Select clinical trials with biologic plausibility to treat PH-HFpEF are summarized in TABLE 2. Currently, there are no pharmacologic agents that are approved to specifically 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 co-morbidities are the mainstays of therapy in HFpEF, and therefore, PH-HFpEF. In addition to normalization of intracardiac and pulmonary pressures and symptom relief, diuresis associated 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 CHAMPION trial was a prospective randomized control trial that enrolled 550 patients with heart failure with both reduced and preserved ejection fraction. Subjects randomized to hemodynamic guided care had substantially more medication titrations (principally diuretics) and experienced a significant reduction in heart failure hospitalizations compared to controls. For one of the first times, subjects with HFpEF and HFrEF showed similar benefit.[47] Post-marketing surveillance study of more than 2000 patients (34% PH-HFpEF) yielded similar results.[48]

The role of mineralocorticoid receptor antagonist spironolactone in HFpEF was studied in the TOPCAT trial.[49] Although the trial failed to meet its primary endpoint, perhaps due to enrollment irregularities in Russia and Georgia, a reduction in HF hospitalizations were noted.[50] 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.[51] Whether this may add particular benefit in PH-HFpEF is unknown. In addition, a large cohort of veterans with pulmonary hypertension suggested a mortality benefit with ace inhibitors and angiotensin-receptor blockade. This included veterans with left heart disease; however, HFpEF was not specifically differentiated in this cohort.[52]

In addition to the optimization of filling pressures, management of the underlying comorbidities like AF, coronary artery disease, systemic hypertension, ~~and~~ metabolic syndrome, and diabetes mellitus is necessary. These factors are prognostically relevant and may be associated with unique and targetable phenotypes.[53,54] The presence of underlying valvular heart disease should be investigated and considered as potential therapeutic targets. 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, though data from a prospective, randomized control trial is needed.[55] With the increasing prevalence of an obesity/metabolic HFpEF phenotype, weight loss management, and aerobic exercise are critical interventions and have both been shown to improve exercise tolerance and reduce body weight in HFpEF.[56]

PAH targeted therapies

Studies of pulmonary vasodilators in PH-HFpEF have largely been disappointing. Although phosphodiesterase-5 (PDE5) inhibitors have proven efficacious in PAH, their role in PH-HFpEF remains unproven. In a prospective placebo-controlled single-center trial of 44 patients with PH-HFpEF defined by elevated pulmonary artery systolic pressure of (PASP) > 40 mm Hg and severe right ventricular dysfunction, sildenafil use compared to placebo showed improvement in pulmonary pressures, RV function and RV dimensions at 6 months.[57] Though it was not enriched for CpcPH, the RELAX study of sildenafil use in subjects with HFpEF did not improve mean pulmonary artery pressure, PAWP, CO, exercise tolerance or VO2.[58,59] In a post hoc analysis of the trial, sildenafil ~~also~~ failed to reduce RV afterload.[60] Similar results were obtained in other studies of ~~sildenafil in~~ predominately IpcPH.[58] In a randomized double-blind placebo-controlled trial of 222 patients (108 ~~patients with~~ CpcPH and 80 IpcPH ~~patients isolated post-capillary~~) with ~~pulmonary hypertension and~~PH-HFpEF related to successfully corrected (at least 1 year before enrollment) valvular heart disease, sildenafil treatment was associated with worse clinical outcomes compared to placebo.[61] The PASSION trial evaluating the effects of tadalafil on HFpEF and CpcPH is currently underway.

While PDE5 inhibitors have failed to show benefit in undifferentiated PH-HFpEF and remain under investigation in CpcPH, another class of medications affecting the same downstream signaling pathways

has also been evaluated. Whereas PDE5 inhibitors prevent the breakdown of cGMP – a vasodilatory and antiproliferative molecular signal –– the soluble guanylyl cyclase stimulators (sGC stimulators) function to directly increase sGC levels in the vasculature and other tissues. DILATE-1 trial evaluated the role of the sGC stimulator riociguat compared to placebo in 39 patients with PH-HFpEF and notably included 5 patients with CpcPH. No significant change in mPAP or PVR at 6 hours was noted in this proof-of-concept study. Subsequent, large prospective randomized trials of sGC-stimulators have shown no benefit in enrolled, undifferentiated HFpEF subjects.[62-64] Finally, several investigations targeting the antagonism of endothelin pathway have been reportedtype A receptors has been undertaken, with consideration for the potential to reduce pulmonary vasoconstriction. A study of the selective endothelin type A (ET_A) receptor sitaxsentan in 192 HFpEF subjects with HFpEF did not meet statistical significance for end points including New York Heart Association (NYHA) functional class, heart failureHF hospitalizations stays, measures of diastolic function, or quality of life questionnaire scores. However, there was a significant increase in exercise tolerance (median treadmill time).[65] Subsequent study of endothelin receptor antagonism in tThe MELODY-1 evaluated the acute role of the endothelin receptor antagonist macitentan in patients with CpcPH identified by diastolic pressure gradient ≥7 mmHg and PVR ≥ 3WU. The trial was powered to evaluate safety endpoints. At 12 weeks, more adverse events were noted with mMacitentan compared to placebo with no improvement in PVR or mean right atrial pressure.[66] Unfortunately, Tthe SERENADE trial, which specifically enrolled patients with HFpEF and pulmonary vascular disease or RV dysfunction, also aimed to test macitentan, but was stopped prematurely (NCT03153111). **At present, PAH-specific therapies should be avoided in PH-HFpEF**.[37] This recognition is relevant given relatively recent real-world evidence suggesting that PAH specific therapies may be prescribed nearly as frequently for PH-LHD as PAH and argues that these therapies are used more frequently than might be assumed for PH-LHD in the rare setting of complex and multifactorial etiologies.[67]

Early phase or investigational therapies

Several on-going pharmacologic and device therapies are being studied in PH-HFpEF. Early phase studies of intra-atrial septal~~shunt~~ devices (IASD) have shown promise in exercise-induced HFpEF but have not specifically enrolled patients with PH-HFpEF.[68,69] In early studies, ~~The use of~~ IASD ~~has been shown to be~~were associated with ~~sustained~~ reduction in PVR, pulmonary Ea and improvement in ~~pulmonary arterial compliance (~~PAC~~)~~ at~~that extends out to~~ 6 months.[69] In an open-label study, the use of IASD was associated with sustained improvements in ~~New York Heart Association~~NYHA functional class (P <0.001), quality of life (P < 0.001) and 6- minute walk distance (P < 0.01).[70] Whether those with CpcPH may be at higher risk of RV dilation or dysfunction after these therapies remain unknown. In a study of 37 patients with group 2 PH with HF with EF of at least 40%, ~~New York Heart Association~~NYHA II or III heart failure, once weekly Levosimendan compared to placebo showed did not significantly reduce the primary endpoint of exercise PAWP (-1.4 mmHg, 95% CI [-7.8, 4.8], p=0.65). However, Levosimendan reduced PAWP measured across all exercise stages (-3.9±2.0 mmHg, p=0.047), and resulted in a 29.3 meter (95% CI [2.5, 56.1], p=0.033) improvement in 6 minute walk distance compared to placebo.[71] Metformin is currently being studied in a phase II trial for PH-HFpEF (NCT03629340) based upon 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.[72] In keeping with the metabolic mechanisms contributing to HFpEF, two large, randomized trials (EMPEROR-Preserved - NCT03057951; DELIVER - NCT03619213) are evaluating the role of SGLT2 inhibitors in HFpEF; results of which could inform the management of PH-HFpEF.[72]

Nitrite, which is reduced to nitric oxide by hemoglobin, is currently being studied in an oral formulation for PH-HFpEF (NCT03015402), having shown promise in an inhaled formulation in PH-HFpEF predominately through improvement in PAC. However, a broader study in HFpEF (uncontrolled for PH) did not show improvement in exercise capacity as assessed by CPET and 6-minute walk distance.[73] Early-phase studies of oral milrinone have also been conducted suggesting improvement in exercise hemodynamics and improved quality of life measures.[74] Finally, PA denervation therapy in CpcPH was studied in the PADN-5 study, which included approximately 400% of subjects with HFpEF. Compared with sildenafil alone, PA denervation resulted in a significant increase in 6-min walk and lower PVR.[75] Additional studies of this potentially promising therapy, such as TROPHY-II (NCT03611270) are underway.

Conclusion:

In HFpEF, the development of pulmonary hypertension 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 have largely been disappointing but novel therapeutic strategies are currently being studied.

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Figure Legend

Figure. Hemodynamic assessment of pulmonary hypertension (PH) due to heart failure with preserved ejection fraction (HFpEF). RV: right ventricular; RHC: right heart catheterization; LHD: left heart disease; PAWP: pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure; CTEPH: chronic thromboembolic PH. a) Pre-test probability of PH-LHD is based on the features presented in table 1. RHC is recommended in intermediate probability when risk factors of pulmonary arterial hypertension/CTEPH are present and/or if there is evidence of right ventricle abnormality. 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 ~~centres~~centers. In patients with intermediate/high probability (table 1) and PAWP between 13 and 15 mmHg, PH-HFpEF is not excluded; provocative testing (tables 2 and 3) should be considered. [#]: for patients with systemic sclerosis, risk factors for CTEPH and/or unexplained dyspnea; [¶]: after [2]; [+]: if PAWP >15 mmHg, LVEDP validation should be considered. Reproduced with permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801897; **DOI:** 10.1183/13993003.01897-2018 Published 24 January 2019.[41]

Table 1. Pre-test probability of left heart disease (LHD) phenotype versus Pulmonary arterial hypertension or pre-capillary PH

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidemia, glucose intolerance/diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention[#]	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*/*e*′ <13
CPET	Mildly elevated V'_E/V'_{CO2} slope; EOV	Elevated V'_E/V'_{CO2} slope *or* EOV	High V'_E/V'_{CO2} slope; no EOV
Cardiac MRI	LA strain or LA/RA >1		No left heart abnormalities

LBBB: left bundle branch block; LVH: left ventricular hypertrophy; RV: right ventricular; LA: left atrial; *E*/*e*′: early mitral inflow velocity/mitral annular early diastolic velocity ratio; CPET: cardiopulmonary exercise testing; V'_E: minute ventilation; V'_{CO2}: carbon dioxide production; EOV: exercise oscillatory ventilation; MRI: magnetic resonance imaging; RA: right atrial. [#]: coronary artery and/or valvular surgical and/or non-surgical procedures, including percutaneous interventions. Reproduced with permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801897; **DOI:** 10.1183/13993003.01897-2018 Published 24 January 2019.[41]

Table 2: Representative Clinical Trials of Pulmonary Hypertension in Heart Failure with Preserved Ejection fraction

Trial	Intervention	Sample Size & Duration	Inclusion Criteria	Study Design	Endpoints	Results
Guazzi M et al *Circulation 2011*	Sildenafil vs. placebo	N=44; 6 and 12 months	LVEF ≥50%, sinus rhythm, PASP ≥40mmHg	Prospective, double-blind, randomized, single-center	Hemodynamics and RV function on echo	Sildenafil: Reductions in mPAP, PVR, RAP, and PAWP with improvements in TAPSE and QOL.
Redfield et al *JAMA 2013* (**RELAX-HF**)	Sildenafil vs. placebo	N = 216, 24 weeks	- pVO_2 <60% normal - NT-proBNP >400 pg/mL or NT-proBNP <400 with mPCWP >20 mmHg	Prospective, randomized, multi-center, double-blind, placebo-controlled	Change in pVO_2 after 24 weeks (*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=0.90*) at 24 weeks
Abraham et al *Circ HF 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 months	- NYHA class III, HF hospitalization in previous 12 months	Prospective, randomized, multi-center, single-blind (post-hoc analysis)	Rate of HF hospitalizations after 6 months	Incidence rate ratio for heart failure hospitalization after 6 months 0.54 for LVEF >40% in treatment vs. control (*P<0.0001*)
Bonderman et al *CHEST 2014* (**DILATE-1)**	Riociguat vs. placebo	N = 477, 6 hours	- LVEF >50%, mPAP ≥ 25 mmHg, PAWP > 15 mmHg (at rest)	Prospective, randomized, multi-center, double-blind, placebo-controlled	Peak decrease in mPAP, change in stroke volume, RV end-diastolic area	Riociguat: peak decrease in mPAP 10 mmHg vs 11 mHg with placebo (*p=0.6*); +9 mL in stroke volume over placebo (P=0.04)
Redfield el al *NEJM 2015* (**NEAT- HFpEF**)	Isosorbide mononitrate vs. placebo (6-week dose-escalation regimen of isosorbide mononitrate with subsequent crossover to the other group for 6 weeks).	N=110; 12 weeks	LVEF ≥50% and objective evidence of heart failure,	Prospective, multi-center, 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
Borlaug et al *JACC 2015*	Intravenous sodium nitrite vs. placebo compared via invasive hemodynamics and measured gas	N=28; 15 minutes after drug administration	LVEF ≥50% and symptoms of HF, PAWP >15 mmHg at rest or ≥25 mmHg with exercise	Prospective, single-center, double-blind, placebo-controlled, parallel-group	Exercise PAWP, mean PAP, mPAP/CO ratio, LVSW Sodium nitrite infusion acutely	Intravenous inorganic nitrite led to acute attenuation of PAWP rise with exercise, reduction in exercise-induced PH, and improved CO reserve.

	exchange 15 min. after administration					
Simon et al *JCI Insight 2016*	Aerosolized sodium nitrite	N=36; 15-60 minutes	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	Baseline hemodynamics prior to and following inhaled NO as well as at 15, minute intervals following 45mg and then 90mg aerosolized sodium nitrite	Aerosolized sodium nitrite was well-tolerated, and in PH-HFpEF (n=10). Compared with other PH groups, PH-HFpEF subjects experienced greatest decrease in PCWP, RAP, RV, and PAP. Pulmonary artery compliance also improved in PH-HFpEF subjects.
Borlaug et al *Circ Res 2016*	Nebulized inhaled sodium nitrite 90mg vs placebo	N=26; hemodynamics at rest, then after 5 minutes of exercise, then 5 minutes after intervention	HFpEF (LVEF ≥50%, PCWP at rest >15 mmHg or with exercise ≥25 mmHg)	Prospective, randomized, single-center, double-blind, placebo-controlled, parallel-group	Primary end point: PCWP during exercise; Secondary end points included changes in PCWP and other hemodynamic measurements	Nebulized inhaled nitrite reduced biventricular pressures and PAPs at rest and during exercise
Vachiéry et al *Eur Respir J 2017* (**MELODY-1**)	Macitentan vs. placebo	N = 63, median treatment duration of 12 vs 12.1 weeks in macitentan vs. placebo groups	- LVEF ≥ vs. < 50% (stratified by LVEF) and CpcPH confirmed by RHC with mPAP >25 mmHg, PAWP >15 mmHg, and < 25 mmHg, and PVR at rest ≥3 WU with DPG ≥7 mmHg	Prospective, randomized, multi-center, double-blind, placebo-controlled	Composite primary endpoint 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 non-significant but numerically greater number of adverse events and serious adverse events with macitentan vs. placebo.
Pieske et al *Eur Heart J 2017* (**SOCRATES-PRESERVED**)	Vericiguat vs. placebo	N=477, 12 weeks	- LVEF > 45%	Prospective, randomized, double-blind, placebo-controlled dose-finding study	Change from baseline NT-proBNP and left atrial volume at 12 weeks	Vericiguat: no significant change in NT-proBNP or LAV at 12 weeks vs. placebo, associated with improved QOL
Reddy et al *Circ Res 2019*	Inhaled Albuterol vs. placebo	N=30, single episode of invasive	LVEF ≥ 50%, resting end-expiratory	Prospective, randomized, double-blind,	Exercise PVR, Resting PVR, rest and	Albuterol: reduction in exercise PVR -0.6 ± 0.5 vs. +0.1 ± 0.7 WU (*p=0.003*).

(**Albuterol in HFpEF**)		hemodynamic exercise-testing	PCWP ≥15 or exercise PCWP ≥ 25 mmHg at 20 W workload	parallel-group, placebo-controlled trial	exercise PCWP, other measures of RV reserve	Albuterol also improved PA compliance, arterial elastance, RV-PA coupling, and cardiac output
Armstrong et al *JAMA 2020* (**VITALITY-HFpEF**)	Vericiguat, up-titrated 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 weeks	LVEF ≥ 45%, NYHA class II-III, within 6 months of a recent decompensation, and elevated natriuretic peptides	Phase 2b randomized, double-blind, placebo-controlled, multicenter trial	Physical limitation score (PLS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ).	Vericiguat: No improvement of PLS of KCCQ compared with placebo; no change in 6-minute walk distance
Udelson et al *JAMA 2020* (**CAPACITY-HFpEF**)	40 mg of praliciguat daily or placebo	N=196, 12 weeks	LVEF ≥ 40%, impaired peak $V'O_2$, and at least 2 conditions associated with NO deficiency	Randomized, double-blind, placebo-controlled, phase 2 trial.	Change from baseline in peak $V'O_2$ in patients who completed at least 8 weeks of assigned dosing	Praliciguat: No difference in peak $V'O_2$ or 6-minute walk distance