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

Journal:	CHEST
Manuscript ID	CHEST-21-0587.R1
Article Type:	CHEST Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Inampudi, Chakradhari; Medical University of South Carolina Silverman, Daniel; Medical University of South Carolina Simon, Marc; University of California San Francisco Leary, Peter; University of Washington, Sharma, Kavita; Johns Hopkins Medicine, Medicine Houston, Brian; Medical University of South Carolina, ; Medical University of South Carolina, Vachiéry, Jean-Luc; Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Department of Cardiology Haddad, Francois; Stanford School of Medicine, Cardiovascular Medicine; Tedford, Ryan; Medical University of South Carolina,
Keywords:	heart failure with preserved ejection fraction, PULMONARY HYPERTENSION, right ventricle, diastolic heart failure, left heart disease
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3 4	1	Manuscript Word count: 3493 references: 75 (max 3500 words; 75 references)
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6	2	Submitted for: CHEST Reviews
7	Z	Submitted for: CHEST Reviews
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9 10	3	
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12	4	Pulmonary Hypertension in the Context of Heart Failure with Preserved Ejection Fraction
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59		ScholarOne - http://mchelp.manuscriptcentral.com/gethelpnow/index.html - (434) 964-4100
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19 20	14	manuscript. He reports general disclosures to include consulting relationships with Abbott. Dr.
20	15	Silverman reports no direct conflicts of interest related to this manuscript. Dr. Simon reports no
22	16	direct conflicts of interest related to this manuscript. He reports general disclosures to include
23	17	consulting relationships with Acceleron, Actelion, United Therapeutics, Altavant Sciences. He
24	18	also does hemodynamic core lab work for Aadi. Dr. Simon is on a steering committee for
25 26	19	Actelion, Complexa. Dr. Simon has received research grant funding from Novartis. Dr. Simon is
20	20	supported by NIH grants R01AG058659 and P01HL103455. Dr. Leary reports no direct conflicts of
28	21	interest related to this manuscript. He reports general disclosures to include research funding
29	22	from the NIH, American Heart Association, Lung LLC, Bayer, and Actelion. He received salary
30	23	support from the CFF Therapeutic Development Network and also has a consulting relationship
31 32	24	with Bayer. Dr. Sharma reports no direct conflicts of interest related to this manuscript. She is a
33	25	consultant and advisory board member to Novartis, Bayer, Bristol Meyers Squibb, and Janssen
34	26	and receives honoraria. Dr. Houston reports no direct conflicts of interest related to this
35	27	manuscript. He reports general disclosures to include research grant and consulting
36	28	relationships with Medtronic. Dr Vachiery reports no direct conflicts of interest related to this
37	29	manuscript. He is a steering committee member for Acceleron, consultant for Acceleron and
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40	31	on Pulmonary Vascular disease at his institution. Outside of this work, he acts as
41	32	consultant/advisor for Altavant, Bayer, Bial Portela, PhaseBio, Respira Therapuetics, and
42	33	Theravance. Dr. Haddad report no conflicts of interest related to this manuscript. Dr. Tedford
43 44	34	reports no direct conflicts of interest related to this manuscript. He reports general disclosures
44	35	to include consulting relationships with Medtronic, Abbott, Aria CV Inc., Arena Pharmaceuticals,
46	36	Acceleron, Eidos Therapeutics, Gradient and United Therapeutics. Dr. Tedford is on a steering
47	37	committee for Medtronic, Acceleron, Itamar and Abbott as well as a research advisory board
48	38	for Abiomed. He also does hemodynamic core lab work for Actelion and Merck.
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50 51	40	
52	41	Key Words/Terms: Heart failure with Preserved Ejection Fraction, Pulmonary Hypertension,
53	71	Rey tronus, remon neur fanare want reserved Ejection fraction, runnonary hypertension,
54	42	Right Ventricle; Diastolic Heart Failure; Left Heart Disease
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1 Abstract

2	Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart
3	failure and is frequently associated with pulmonary hypertension (PH). PH-HFpEF may be
4	difficult to distinguish from pre-capillary forms of PH, though this distinction is crucial as
5	therapeutic pathways are divergent for the two conditions. A comprehensive and systematic
6	approach utilizing history, clinical exam, non-invasive and invasive evaluation with and without
7	provocative testing may be necessary for accurate diagnosis and phenotyping. Once diagnosed,
8	PH-HFpEF can be subdivided into isolated post-capillary pulmonary hypertension (IpcPH) and
9	combined post- and pre-capillary pulmonary hypertension (CpcPH) based on the presence or
10	absence of elevated pulmonary vascular resistance (PVR). CpcPH portends a worse prognosis
11	than IpcPH. Despite its association with reduced functional capacity and quality of life, heart
12	failure hospitalizations, and higher mortality, therapeutic options focused on pulmonary
13	hypertension for PH-HFpEF remain limited. In this review, we aim to provide an updated
14	overview on clinical definitions and hemodynamically characterized phenotypes of PH,
15	pathophysiology, therapeutic strategies, and ongoing challenges in this patient population.
16	Abstract word count: 169 (max 250 words)
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1 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 \ge 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

dysfunction and are better predictors of outcomes in PH-HFpEF, they are not helpful in distinguishing

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

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

development of a pre-capillary component due to pulmonary vasoconstriction, which is at least partially

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functional, and in some cases, structural remodeling of the pulmonary veins, capillaries, and arteries

elevation in pressure.¹³ Ultimately, elevated pressure and/or poor cardiac output leads to the

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

compared to pre-capillary parameters. Although they are associated with more significant RV

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IpcPH and CpcPH.8

Pathophysiology

occur.14,15

Pulmonary vasculature

regurgitation and low cardiac output.¹¹

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3 4	1	Several factors contribute to the functional pathology in PH-HFpEF. Left atrial hypertension
5 6	2	causes stress failure of the alveolar-capillary junction with the development of pulmonary edema. The
7 8	3	edema activates inflammatory mediators that increases endothelin-1 expression, decrease in nitric
9 10 11	4	oxide and natriuretic peptide activity. This may also lead to fibroblast proliferation, occlusion of the
12 13	5	lumen and thickening of the alveolar septa. The remodeling is reflected by impairment of gas exchange,
14 15	6	contributing to dyspnea and hypoxemia. ^{16,17} Obokata and colleagues, in a prospective hemodynamic
16 17	7	study of 38 patients with HFpEF with 20 controls, found that the HFpEF subjects with PH displayed
18 19 20	8	activation of endothelin and adrenomedullin neurohormonal pathways. The C-terminal pro-endothelin-
20 21 22	9	1 and MR—pro ADM levels were strongly correlated with mean PA pressure (r = 0.73 and 0.65, both P <
23 24	10	0.0001) and PAWP (r = 0.67 and 0.62, both P < 0.0001) and inversely correlated with PAC (r = -0.52 and -
25 26	11	0.43, both P < 0.001). ¹⁸ As mentioned above, left atrial hypertension also lowers PAC, making the
27 28 29	12	vasculature stiff, increasing pulmonary pulse pressure, and indirectly increasing PVR. Furthermore,
30	13	engorged lymphatics and edema may compress small distal lung arterioles, contributing to the pre-
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32 33	14	capillary component. ¹⁹
32 33 34 35	14 15	capillary component. ¹⁹ The above factors and others eventually promote remodeling in the pulmonary arteries and
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32 33 34 35 36 37 38 39 40	15	The above factors and others eventually promote remodeling in the pulmonary arteries and
32 33 34 35 36 37 38 39 40 41 42	15 16	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.
32 33 34 35 36 37 38 39 40 41 42 43 44	15 16 17	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
32 33 34 35 36 37 38 39 40 41 42 43	15 16 17 18	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
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	15 16 17 18 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
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32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 3 54	15 16 17 18 19 20 21	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
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	15 16 17 18 19 20 21 21	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

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3 4	1	baseline were protective of future heart failure events and were also associated with smaller LV size and
5 6	2	higher LV ejection fraction. ²² Animal models of HFpEF and specifically PH-HFpEF have recently been
7 8	3	developed, and may ultimately improve our understanding of the development of pulmonary vascular
9 10 11	4	disease as well as heart dysfunction. ^{23,24}
12 13 14	5	
14 15 16 17	6	Right Ventricle
18 19 20	7	The function of the right ventricle (RV) is likely the most important prognostic factor in PH-
20 21 22	8	HFpEF. ^{25,26} RV diastolic dysfunction may occur early in the disease course. In a study of 24 compensated
23 24	9	HFpEF patients with preserved CO and mildly elevated pulmonary pressures and 9 patients without
25 26 27	10	heart failure symptoms who underwent RV pressure-volume measurement, increased RV stiffness and
27 28 29	11	prolonged RV relaxation was present, though RV systolic function was preserved. ²⁷ Later in the disease,
30 31	12	overt RV systolic dysfunction can develop. ²⁸ RV systolic function depends on both the afterload imposed
32 33	13	on it from the pulmonary circulation and intrinsic myocardial contractility. PVR and PAC both contribute
34 35 36	14	to increased resistive and pulsatile afterload. ²⁹ Chronically elevated afterload results in RV hypertrophy
37 38	15	as a compensatory mechanism. With sustained afterload, chamber dilation, tricuspid regurgitation,
39 40 41	16	fibrosis, and loss of contractility, ultimately irreversible decrease in RV function ensues. ²⁸ The processes
41 42 43	17 18	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
44 45	18	in HFpEF patients and may contribute to the inflammatory milieu, right ventricular fibrosis, and even
46 47 48	20	myocyte dysfunction. In 63 HFpEF patients with RV septal endomyocardial biopsy, those with marked
49 50	21	obesity exhibited more depressed RV systolic sarcomere function yet less passive myocyte stiffening. ³⁰
51 52	22	Thus, although not well characterized, it appears certain patient phenotypes may have an "at-risk" RV
53 54	23	less able to compensate for increases in afterload.
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1	RV-LV Interactions and Atrial Fibrillation
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2 Ventricular interaction may play a significant role in the pathophysiology and functional limitations 3 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 4 5 HFpEF without PH and IpcPH, PAWP typically increases out of proportion to RAP during exertion, 6 increasing the LV transmural pressure. However, CpcPH patients demonstrate greater increases in RAP 7 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 8 9 reserve and more significant reductions in aerobic capacity.³¹ Worsening pulmonary vascular disease, 10 right heart failure and pericardial restraint has also been described in a sub-phenotype of HFpEF with 11 permanent atrial fibrillation. Reduced left atrial compliance and impaired mechanics are associated with 12 increasing burden of atrial fibrillation. Atrial fibrillation and left atrial dysfunction appear to be strong 13 promotors of PH in HFpEF. ³²

14

15 Diagnosis of PH-HFpEF

16 The evaluation of a patient with suspected PH in HFpEF requires comprehensive clinical, 17 echocardiographic, and hemodynamic assessments. A high degree of suspicion is necessary for the 18 diagnosis of PH-HFpEF, which can easily be misdiagnosed as PAH.² Factors associated with PH-LHD 19 include the presence of AF, left atrial enlargement, age > 60 years, coronary artery disease, and BMI > 20 30 kg/m2 (TABLE 1), and these factors help determine the pre-test probability of PH-LHD. The physical 21 exam and chest X-ray provide signs of fluid retention or signs of RV failure. Transthoracic 22 echocardiography (TTE) serves as an excellent screening tool and is the first step in the evaluation of 23 patients suspected of PH. While elevated PA systolic pressures (PASP) values derived from Doppler

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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

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3 4	1	such, particularly among individuals with mild PH, the pretest probability for PH-LHD should be higher.
5 6	2	With the use of diuretics and afterload reduction, it is possible to lower PAWP into the normal range
7 8 9	3	despite the presence of significant LHD. This has led some experts to suggest a diagnostic RHC be
9 10 11	4	performed before volume status optimization. ¹¹ When there is an intermediate to high probability of
12 13	5	PH-LHD, but hemodynamics meet criteria for a pre-capillary disease, additional testing should be
14 15	6	considered. FIGURE outlines a suggested algorithm from the 6 th WSPH. ³⁷ Given the practical and
16 17	7	technical challenges with exercise, a fluid challenge is generally the preferred way to detect occult left
18 19 20	8	heart disease, specifically when differentiating group 1 from group 2 PH. A PAWP >18 mm Hg
20 21 22	9	immediately following the administration of 500 cc of normal saline over 5 minutes (or weight-based
23 24	10	dosing of 7 cc/kg) is considered abnormal and suggestive of PH-LHD. ^{37,4243} At expert centers, cycle
25 26	11	ergometry may be performed as an alternative, with a cutoff of PAWP ≥25 mmHg during supine exercise
27 28	12	(or ≥20 mmHg during upright exercise) generally accepted as representing the presence of left heart
29 30 31	13	disease. It should be noted, however, that pressures taken during exercise may vary significantly
32 33	14	depending on how the PAWP is measured in respect to the respiratory cycle. ³⁶ . The position statement
34 35	15	from ERS recommends averaging over the respiratory cycle during exercise. ⁴⁴ The multi-point slope of
36 37	16	PAWP and cardiac output may prove to be a more reliable measure to discriminate between occult LHD
38 39 40	17	and normal left-sided response to exercise, with > 2 mm Hg/L/min being considered abnormal. 45 It may
40 41 42	18	also be less prone to issues with respiratory swings if all pressures are measured in a consistent
43 44	19	manner. ⁴⁶
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49 50 51	21	Therapeutic strategies
52 53	22	The significant gaps in understanding the complex pathobiology processes and comorbidities
54 55 56 57	23	that complicate or drive the development and progression of PH has rendered the search for effective
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1	therapies particularly difficult. Furthermore, PH may represent a marker of disease severity rather than
2	an optimal target for therapy. Select clinical trials with biologic plausibility to treat PH-HFpEF are
3	summarized in TABLE 2. Currently, there are no pharmacologic agents that are approved to specifically
4	target PH in the setting of HFpEF, a result of disappointing results from these numerous studies. Loop
5	diuretics for relief of volume overload and concomitant treatment of co-morbidities are the mainstays of
6	therapy in HFpEF, and therefore, PH-HFpEF. In addition to normalization of intracardiac and pulmonary
7	pressures and symptom relief, diuresis associated increases in PAC reduce pulsatile loading to the RV.
8	The use of pulmonary artery monitoring devices may be particularly useful to achieve and maintain
9	euvolemia. The CHAMPION trial was a prospective randomized control trial that enrolled 550 patients
10	with heart failure with both reduced and preserved ejection fraction. Subjects randomized to
11	hemodynamic guided care had substantially more medication titrations (principally diuretics) and
12	experienced a significant reduction in heart failure hospitalizations compared to controls. For one of the
13	first times, subjects with HFpEF and HFrEF showed similar benefit. ⁴⁷ Post-marketing surveillance study of
14	more than 2000 patients (34% PH-HFpEF) yielded similar results. ⁴⁸
15	The role of mineralocorticoid receptor antagonist spironolactone in HFpEF was studied in the
16	TOPCAT trial. ⁴⁹ Although the trial failed to meet its primary endpoint, perhaps due to enrollment
17	irregularities in Russia and Georgia, a reduction in HF hospitalizations were noted. ⁵⁰ Animal and
18	preliminary human data in PAH suggest that aldosterone antagonists may reduce pulmonary
19	vasoconstriction by attenuating the adverse effects of hyperaldosteronism on endothelin type-B
20	receptor function in pulmonary endothelial cells. ⁵¹ Whether this may add particular benefit in PH-HFpEF
21	is unknown. In addition, a large cohort of veterans with pulmonary hypertension suggested a mortality
22	benefit with ace inhibitors and angiotensin-receptor blockade. This included veterans with left heart
23	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

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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 \geq 7 mmHg and PVR \geq 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

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

3 Early phase or investigational therapies

4 Several on-going pharmacologic and device therapies are being studied in PH-HFpEF. Early 5 phase studies of intra-atrial septal devices (IASD) have shown promise in exercise-induced HFpEF but 6 have not specifically enrolled patients with PH-HFpEF.^{68,69} In early studies, IASD were associated with 7 reduction in PVR, pulmonary Ea and improvement in PAC at 6 months.⁶⁹ In an open-label study, the use 8 of IASD was associated with sustained improvements in NYHA functional class (P < 0.001), guality of life (P < 0.001) and 6- minute walk distance (P < 0.01).⁷⁰ Whether those with CpcPH may be at higher risk of 9 10 RV dilation or dysfunction after these therapies remain unknown. In a study of 37 patients with group 2 11 PH with HF with EF of at least 40%, NYHA II or III heart failure, once weekly Levosimendan compared to 12 placebo showed did not significantly reduce the primary endpoint of exercise PAWP (-1.4 mmHg, 95% CI 13 [-7.8, 4.8],p=0.65). However, Levosimendan reduced PAWP measured across all exercise stages (-3.9±2.0 14 mmHg, p=0.047), and resulted in a 29.3 meter (95% CI [2.5, 56.1], p=0.033) improvement in 6 minute 15 walk distance compared to placebo.⁷¹ Metformin is currently being studied in a phase II trial for PH-16 HFpEF (NCT03629340) based upon several lines of evidence including improved heart failure outcomes 17 in patients with type 2 diabetes in several large observational cohorts, decrease in cardiac work 18 associated with reduced myocardial glucose uptake and fatty acid oxidation, and improvements 19 metabolism in both skeletal muscle and pulmonary vascular smooth muscle via upregulation of the 20 SIRT3-AMPK-Glut4 pathway.⁷² In keeping with the metabolic mechanisms contributing to HFpEF, two 21 large, randomized trials (EMPEROR-Preserved - NCT03057951; DELIVER - NCT03619213) are evaluating 22 the role of SGLT2 inhibitors in HFpEF; results of which could inform the management of PH-HFpEF.

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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 Earlyphase 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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3	1		Improves Hemodynamics and Eversice Telerance in DH HENEE, Results from the HELD DH HENEE
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1 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

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3 4	Abbreviation List
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7 8	HFpEF: heart failure with preserved ejection Fraction
9	PH: pulmonary hypertension
10 11	IpcPH: isolated post-capillary pulmonary hypertension
12 13	CpcPH: combined post- and pre-capillary pulmonary hypertension
14 15	WSPH: World Symposium on Pulmonary Hypertension
16	PAH: Pulmonary Arterial Hypertension
17 18	mPAP: mean pulmonary artery pressure
19 20	LHD: left heart disease
21 22	PAWP: pulmonary artery wedge pressure
23 24	CO: cardiac output
25	WU: Wood units
26 27	
28 29	RHC: right heart catheterization
30 31	PVR: pulmonary vascular resistance
32	PAC: pulmonary arterial compliance
33 34	Ea: pulmonary arterial elastance
35 36	RV: right ventricular
37 38	BMI: body mass index
39 40	TTE: transthoracic echocardiogram
41	PASP: pulmonary artery systolic pressure
42 43	AF: atrial fibrillation
44 45	PDE5: phosphodiesterase-5
46 47	sGC: soluble guanylyl cyclase
48	CPET: Cardiopulmonary Exercise Test
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Table 1. Pre-test probability	v of left heart disease (Ll	HD) 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 strai
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; <i>E/e</i> ′ <13
	Mildly		
CPET	elevated $V'_{\rm E}/V'_{\rm CO2}$ slope; EOV	Elevated V'_{E}/V'_{CO2} slope or EOV	High V'_{E}/V'_{CO2} slope; no EO
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

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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 <i>Circulation 2011</i>	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 <i>JAMA 2013</i> (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 (<i>primary</i>)	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) (<i>p</i> =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 hear failure hospitalization after 6 months 0.54 for LVEF >40% in treatment vs. control (<i>P</i> <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 placel (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 exercis 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-induce PH, and improved CO reserve.

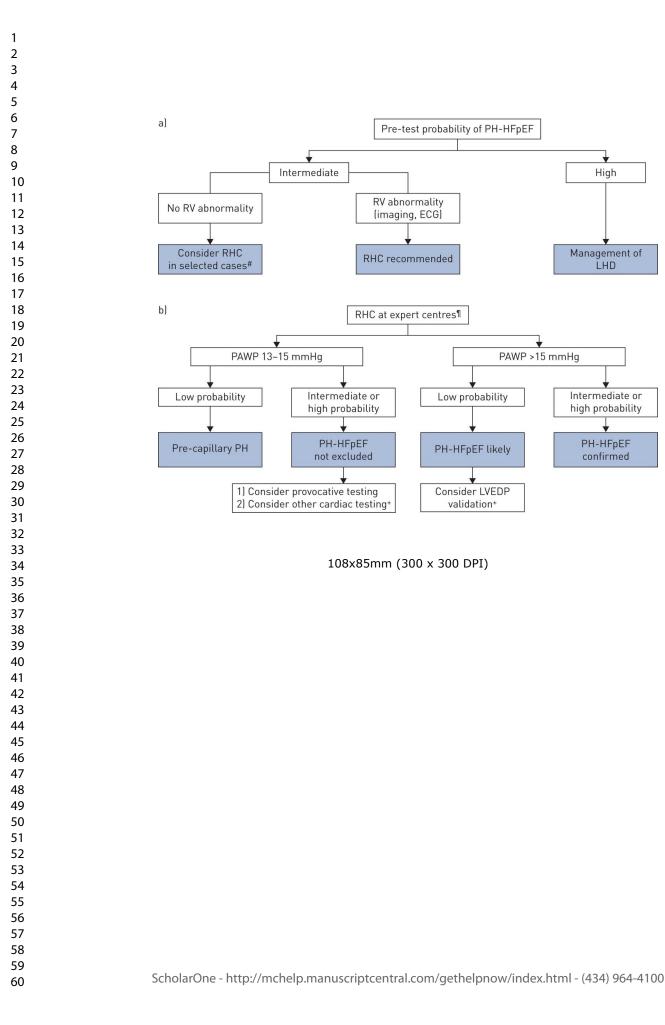
	exchange 15 min. after administration					
Simon et al JCI Insight 2016	Aerosolized sodium nitrite	N=36; 15-60 minutes	WHO group I, II, and III PH. Exploratory for Group 2 PH (PH- HFpEF), change in PVR for Group 1 and Group 3 PH	Prospective, open-label, safety and efficacy	Baseline hemodynamics prior 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 <i>Circ Res 2016</i>	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 E <i>ur Respir J 2017</i> [MELODY-1]	Macitentan vs. placebo	N = 63, median treatment duration of 12 vs 12.1 weeks in macitentan vs. placebo groups	- LVEF \geq vs. < 50% (stratified by LVEF) and CpcPH confirmed by RHC with mPAP >25 mmHg, PAWP >15 mmHg, and < 25 mmHg, and PVR at rest \geq 3 WU with DPG \geq 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 LA 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 \pm 0.5 vs. +0.1 \pm 0.7 WU (<i>p</i> =0.003).

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(Albuterol in		hemodynamic	PCWP ≥15 or	parallel-group,	exercise PCWP,	Albuterol also improved PA
HFpEF)		exercise-	exercise PCWP	placebo-	other measures	compliance, arterial
		testing	≥ 25 mmHg at	controlled trial	of RV reserve	elastance, RV-PA coupling,
			20 W workload			and cardiac output
Armstrong et al	Vericiguat, up-titrated	N=789, 24	LVEF ≥ 45%,	Phase 2b	Physical	Vericiguat: No improvement
JAMA 2020 (VITALITY-HFpEF)	to 15-mg (n = 264) or 10-mg (n = 263) daily	weeks	NYHA class II-III, within 6 months	randomized, double-blind,	limitation score (PLS) of the	of PLS of KCCQ compared with placebo; no change in 6
	oral dosages,		of a recent	placebo-	Kansas City	minute walk distance
	compared with		decompensation,	controlled,	Cardiomyopathy	
	placebo ($n = 262$) and		and elevated	multicenter trial	Questionnaire	
	randomized 1:1:1.		natriuretic		(KCCQ).	
			peptides			
Jdelson et al	40 mg of praliciguat	N=196, 12	LVEF ≥ 40%,	Randomized,	Change from	Praliciguat: No difference in
IAMA 2020	daily or placebo	weeks	impaired peak	double-blind,	baseline in peak	peak VO_2 or 6-minute walk
CAPACITY-			VO ₂ , and at least	placebo-	Vo ₂ in patients	distance
HFpEF)			2 conditions	controlled,	who completed	
			associated with	phase 2 trial.	at least 8 weeks	
			NO deficiency		of assigned dosing	



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3 4	1	Manuscript Word count: 3493 references: 75 (max 3500 words; 75 references)
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6	2	Submitted for: CHEST Reviews
7	2	Submitted for. Cirls r Reviews
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9 10	3	
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12	4	Pulmonary Hypertension in the Context of Heart Failure with Preserved Ejection Fraction
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19	13	manuscript. He reports general disclosures to include consulting relationships with Abbott. Dr.
20	14	Silverman reports no direct conflicts of interest related to this manuscript. Dr. Simon reports no
21	15	direct conflicts of interest related to this manuscript. He reports general disclosures to include
22		consulting relationships with Acceleron, Actelion, United Therapeutics, Altavant Sciences. He
23 24	17	
25	18	also does hemodynamic core lab work for Aadi. Dr. Simon is on a steering committee for
26	19 20	Actelion, Complexa. Dr. Simon has received research grant funding from Novartis. Dr. Simon is
27	20	supported by NIH grants R01AG058659 and P01HL103455. Dr. Leary reports no direct conflicts of
28	21	interest related to this manuscript. He reports general disclosures to include research funding
29 30	22	from the NIH, American Heart Association, Lung LLC, Bayer, and Actelion. He received salary
31	23	support from the CFF Therapeutic Development Network and also has a consulting relationship
32	24	with Bayer. Dr. Sharma reports no direct conflicts of interest related to this manuscript. She is a
33	25	consultant and advisory board member to Novartis, Bayer, Bristol Meyers Squibb, and Janssen
34	26	and receives honoraria. Dr. Houston reports no direct conflicts of interest related to this
35 36	27	manuscript. He reports general disclosures to include research grant and consulting
37	28	relationships with Medtronic. Dr Vachiery reports no direct conflicts of interest related to this
38	29	manuscript. He is a steering committee member for Acceleron, consultant for Acceleron and
39	30	Bayer within the framework of this manuscript. He is the holder of the Janssen Research Chair
40	31	on Pulmonary Vascular disease at his institution. Outside of this work, he acts as
41 42	32	consultant/advisor for Altavant, Bayer, Bial Portela, PhaseBio, Respira Therapuetics, and
42	33	Theravance. Dr. Haddad report no conflicts of interest related to this manuscript. Dr. Tedford
44	34	reports no direct conflicts of interest related to this manuscript. He reports general disclosures
45	35	to include consulting relationships with Medtronic, Abbott, Aria CV Inc., Arena Pharmaceuticals,
46	36	Acceleron, Eidos Therapeutics, Gradient and United Therapeutics. Dr. Tedford is on a steering
47 48	37	committee for Medtronic, Acceleron, Itamar and Abbott as well as a research advisory board
40 49	38	for Abiomed. He also does hemodynamic core lab work for Actelion and Merck.
50	39	
51	40	
52	41	Key Words/Terms: Heart failure with Preserved Ejection Fraction, Pulmonary Hypertension,
53 54	42	Right Ventricle; Diastolic Heart Failure; Left Heart Disease
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1 Abstract

2	Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart
3	failure and is frequently associated with pulmonary hypertension (PH). PH-HFpEF may be
4	difficult to distinguish from pre-capillary forms of PH, though this distinction is crucial as
5	therapeutic pathways are divergent for the two conditions. A comprehensive and systematic
6	approach utilizing history, clinical exam, non-invasive and invasive evaluation with and without
7	provocative testing may be necessary for accurate diagnosis and phenotyping. Once diagnosed,
8	PH-HFpEF can be subdivided into isolated post-capillary pulmonary hypertension (IpcPH) and
9	combined post- and pre-capillary pulmonary hypertension (CpcPH) based on the presence or
10	absence of elevated pulmonary vascular resistance (PVR). CpcPH portends a worse prognosis
11	than IpcPH. Despite its association with reduced functional capacity and quality of life, heart
12	failure hospitalizations, and higher mortality, therapeutic options focused on pulmonary
13	hypertension for PH-HFpEF remain limited. In this review, we aim to provide an updated
14	overview on clinical definitions and hemodynamically characterized phenotypes of PH,
15	pathophysiology, therapeutic strategies, and ongoing challenges in this patient population.
16	Abstract word count: 1698 (max 250 words)
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3 4 5	1	Introduction and Epidemiology
5 6 7	2	Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure
8 9	3	and is frequently complicated by the development of pulmonary hypertension (PH). The prevalence of
10 11	4	PH in HFpEF varies widely based on population, study design, the definition of PH, and diagnostic
12 13	5	modalities, with some estimates ranging from 30-80%. ¹ The hemodynamic and functional alterations
14 15 16	6	that occur in the setting of abnormal cardiovascular structure and function contribute to the
17 18	7	development of PH. ² PH-HFpEF is associated with dyspnea, ventilatory impairments, reduction in
19 20	8	aerobic capacity, high symptom burden, an increase in hospitalizations, and higher mortality. ³ The
21 22	9	present paper on PH-HFpEF reviews the definition and classification, pathophysiology, challenges with
23 24 25	10	diagnosis, and current and emerging treatment strategies.
26 27	11	
28 29	11	
30	12	Definition and Classification
31 32	13	
33 34	14	Since the initial description of PH in 1940, the novel mechanistic insights by Paul Wood from
35 36 37	15	1956-1958, and the first version of clinical classification in 1973, the diagnosis has gone through a series
37 38 39	16	of iterative changes. Based partially on expert opinion and to minimize the chances of overdiagnosis of
40 41	17	pulmonary arterial hypertension (PAH), a mean pulmonary artery pressure (mPAP) of \geq 25mmHg was
42 43	18	first used to define PH. At the proceedings of the fourth World Symposium of Pulmonary Hypertension
44 45	19	(WSPH), PH due to left heart disease (LHD) was divided into passive versus reactive or "out-of-
46 47 48	20	proportion" PH based on the transpulmonary gradient (TPG): calculated as mean pulmonary artery
49 50	21	pressure (mPAP) minus pulmonary arterial wedge pressure (PAWP). A TPG > 12mmHg was
51 52	22	recommended as a marker indicative of pulmonary vascular remodeling and was commonly used to
53 54	23	distinguish passive from reactive PH; however, the specificity of this approach was later questioned as
55 56	24	the gradient may be influenced by changes in cardiac output (CO), recruitment and distension of
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1 pulmonary vessels, and loading conditions. In 2013, the diastolic pressure gradient (DPG; diastolic 2 pulmonary artery pressure minus PAWP) was proposed to distinguish isolated post-capillary PH (IpcPH) 3 from combined post- and pre-capillary (CpcPH). The DPG may be less influenced by flow and loading 4 conditions, and a DPG < 7 mmHg defined IpcPH whereas \geq 7 mmHg defined CpcPH; however, due to 5 concerns related to measurement fidelity and mixed reports on its prognostic utility, DPG also fell out of 6 favor. This has been reflected in the last international guidelines on PH, in which CpcPH was defined as 7 DPG > 7 mm Hg and/or PVR > 3 WU. 8 The hemodynamic definition of pulmonary hypertension -due to left heart disease (PH-LHD), 9 also classified as World Health Organization (WHO) Group 2 PH, has been proposed during the 6th WSPH 10 as a mPAP >-20 mm Hg and a PAWP >-15mmHg as measured by right heart catheterization (RHC).⁴ The 11 lower threshold of mPAP is based on reference datae in healthier controls and was selected to 12 harmonize with the new definition of PAH.⁵ As these definitions and concepts rely heavily on 13 hemodynamic definition, proper measurements of cardiac output and pulmonary pressures become

14 essential. While directly measured Fick, cardiac output remains the gold standard measurement, the use

15 <u>of a metabolic cart for indirect calorimetry is not widespread in clinical practice. More often, indirect or '</u>

16 <u>assumed' Fick is utilized, though it has been demonstrated that its</u> Wolf et al. and others have

17 demonstrated that use of the assumed Fick may lead to inaccurate measures of cardiac output_and so

18 <u>the</u> thermodilution technique is preferred even in the setting of tricuspid regurgitation and low cardiac

19 output Among those with recognized PH-LHD, individuals are now stratified into IpcPH and CpcPH solely

21 defined by PVR, is associated with reduced RV function and increased morbidity and mortality compared

based on <u>pulmonary vascular resistance</u> (PVR), defined as TPG/CO, of $< \text{ or } \ge 3$ Wood units (WU). -CpcPH,

- to IpcPH.⁶ A recent analysis of 40,082 patients undergoing RHC in the U.S Veterans Affairs health-care
- 23 system found excess adjusted all-cause mortality began at a threshold of 2.2 WU, suggesting even lower
- 24 PVR values may be clinically relevant.⁷ <u>Finally, PAC, pulmonary arterial compliance (PAC), (estimated as</u>

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3 4	1	stroke volume/PA pulse pressure), and pulmonary arterial elastance (Ea), defined as systolic PA
5 6	2	pressure/stroke volume, are both impacted by left atrial hypertension and PVR. They may better
7 8	3	represent the total RV afterload compared to pre-capillary parameters. Although they are associated
9 10	4	with more significant RV dysfunction and are better predictors of outcomes in PH-HFpEF, they are not
11 12 13	5	helpful in distinguishing IpcPH and CpcPH. ⁸
14 15 16	6	As these definitions and concepts rely heavily on hemodynamic definition, proper
17 18	7	measurements of both pressures and cardiac output become essential. While directly measured cardiac
19 20	8	output remains the gold standard measurement, the use of a metabolic cart for indirect calorimetry is
21 22 23	9	not widespread in clinical practice. More often, indirect or 'assumed' Fick is utilized, though it has been
23 24 25	10	demonstrated that its use may lead to inaccurate measures of cardiac output in the setting of heart
26 27	11	failure and PH. ^{9,10} Therefore, thermodilution technique is preferred even in the setting of tricuspid
28 29	12	regurgitation and low cardiac output. ¹¹
30 31 32	13	Pulmonary arterial compliance (PAC) (estimated as stroke volume/PA pulse pressure), a global
33 34	14	parameter of pulmonary artery distensibility, and pulmonary arterial elastance (Ea), defined as systolic
35 36 37	15	PA pressure/stroke volume, may better represent the total RV afterload compared to pre-capillary
38 39	16	parameters. Although they are associated with more significant RV dysfunction and are better
40 41	17	predictors of outcomes in PH-HFpEF, they are not helpful in distinguishing IpcPH and CpcPH.
42 43 44	18	
45 46 47	19	Pathophysiology
48 49 50	20	Pulmonary vasculature
51 52 53	21	In patients with HFpEF, abnormal myocardial active relaxation and increased passive stiffness of
54 55 56 57	22	the left ventricle leads to elevation in left ventricular and thus left atrial pressures to maintain cardiac
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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 <u>at least partially</u> 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 -leading 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 maycan compress small distal lung arterioles, increasing PVRcontributing 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),

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2 3	1	impacted directly by left atrial hypertension. and pulmonary arterial elastance (Ea), defined as systolic
4 5 6	2	PA pressure/stroke volume, may better represent the total RV afterload compared to pre-capillary
7 8	3	parameters. Although they are associated with more significant RV dysfunction and are better
9 10 11	4	predictors of outcomes in PH-HFpEF, they are not helpful in distinguishingwhich determines the blood
12 13	5	storage capacity of the pulmonary circulation, is also impacted directly by left atrial hypertension. In
14 15	6	healthy individuals, the principal determinant of compliance is PVR, and thus, a linear relationship exists
16 17	7	between pulmonary artery systolic, mean, and diastolic pressures. However, as pressure is transmitted
18 19 20	8	backward from the left heart, compliance declines for any given resistance. As compliance declines,
21 22	9	pulmonary pulse pressure and mPAP increase due to a rise in systolic pulmonary artery pressure relative
23 24	10	to diastolic pressure, further contributing to <u>IpcPH and CpcPH.</u> the pre-capillary component.
25 26 27	11	The above factors and others eventually promote remodeling in the pulmonary arteries and
28 29 30 31	12	veins with various combinations of intimal proliferation, medial hypertrophy, and adventitial thickening.
	13	In a landmark study of patients with PH- <u>HFpEFLHD</u> , <u>Fayyaz, et al Padang R et al</u> found evidence of
32 33 34	14	significant venous remodeling, with similar pathologic appearance to pulmonary veno-occlusive disease.
35 36	15	In keeping, it was venous and intermediate vessel changes that were venous medial hypertrophy was
37 38	16	the most common pathologic finding and correlated more closely associated with with higher
39 40	17	pulmonary pressures than the arterial remodeling. ²⁰ ²⁰ The Pulmonary artery systolic pressure more
41 42 43	18	correlated with venous or small indeterminate vessels percent intimal thickness. In 30 PH-HF who
44 45	19	underwent RHC, numerically stronger association noted between transpulmonary gradient (TPG) and
46 47	20	pulmonary vascular remodeling. Additionally, the venous and small vessel intimal thickening was noted
48 49 50	21	to be more severe than arterial intimal thickening in PH-HFpEF. In the spectrum of PH-HFpEF, a subset of
50 51 52	22	patients exhibits a unique phenotype that shares biological overlap with PAH. When evaluated at the
53 54	23	cellular level, the pathways involved in lung microvasculature remodeling have also been shown to
55 56	24	contribute to left atrial fibrosis. The new cell lines 'aerocyte' and 'general' capillary (gCap), as their roles
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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" theoptimize 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}

16 Right Ventricle

The function of the right ventricle (RV) is likely the most important prognostic factor in PHHFpEF.^{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

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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 seenplay 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

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2		12
6 F	1	with the severity of pulmonary vascular disease present. ³¹ Worsening pulmonary vascular disease, right
) ,	2	heart failure and pericardial restraint has also been described in a sub-phenotype of HFpEF with
	3	permanent atrial fibrillation. Reduced left atrial compliance and impaired mechanics are associated with
0 1	4	increasing burden of atrial fibrillation. Atrial fibrillation and left atrial dysfunction appear to be strong
2 3 4	5	promotors of PH in HFpEF. ³²
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	2	Diagnosis of PH-HFpEF
	3	The evaluation of a patient with suspected PH in HFpEF requires comprehensive clinical,
) 1	4	echocardiographic, and hemodynamic assessments. A high degree of suspicion is necessary for the
2 3	5	diagnosis of PH-HFpEF, which can easily be misdiagnosed as PAH. ² Factors associated with PH-LHD
4 5	6	include the presence of AF, left atrial enlargement, age > 60 years, coronary artery disease, and BMI >
5 7 8	7	30 kg/m2 (TABLE 1), and these factors help determine the pre-test probability of PH-LHDThe physical
	8	exam and chest X-ray provide signs of fluid retention or signs of RV failure. Transthoracic
1 2	9	echocardiography (TTE) serves as an excellent screening tool and is the first step in the evaluation of
3 4	10	patients suspected of PH. TTE has been shown to have moderate precision for identifying PH and
5 7	11	determining severity. While elevated PA systolic pressures (PASP) values derived from Doppler
, 3 9	12	echocardiography correlate with the presence of elevated pulmonary pressures, the accuracy of PASP
) 1	13	estimates are variable between studies ³³ Better accuracy can be observed when using modal frequency
2 3	14	for velocity estimates, optimizing insonation angle and resisting the temptation of estimating pressures
4 5	15	in the presence of an incomplete signal ³⁴ Pulmonary function testing <u>-can identify associated lung</u>
5 7 3	16	disease and aid in PH classification. Cardiopulmonary exercise testing (CPET) may be diagnostically
9)	17	useful as identify WHO Group 3 PH, higher Ve/VCO2 slope cardiopulmonary exercise testing_is
1 2	18	associated with more significant pre-capillary disease whereas the presence of exercise oscillatory
3 4 -	19	ventilation (EOV) is more common in isolated heart failure. ³⁵ can provide data on VE/VCo2 slope that
5 7	20	has been correlate with outcome in CPcPH, and cardiac magnetic resonance imaging can also aid in
3 9	21	diagnosis in selected patients. Individuals with CpcPH should be ruled out for chronic thromboembolic
) 1	22	disease and other conditions associated with pre-capillary disease as guided by history, physical exam
2 3	23	and diagnostic evaluation.
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Though TTEechocardiography 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

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1	group 2 PH-at-rest in this situation. A PAWP >-18 mm Hg immediately following the administration of
2	500 cc of normal saline over 5 minutes <u>(or in some cases using a weight-based dosing of {7 cc/kg) is</u>
3	considered abnormal and suggestive of PH-LHD. ^{37,4243} At expert centers, upright or supine cycle
4	ergometry may be performed as an alternative, with a cutoff of PAWP ≥-25 mm-Hg during supine
5	exercise (or ≥20 mmHg during upright exercise) generally accepted as representing the presence of left
6	heart disease. It should be noted, however, that pressures taken during exercise may vary significantly
7	based on whether measurement is performed at end-expiration, or during the course of the respiratory
8	cycle as advised in the 2015 ESC/ERS guidelines depending on how the PAWP is measured in respect to
9	the respiratory cycle. ³⁶ . The position statement from the 2015 ESC/ERS recommends averaging over the
10	respiratory cycle during exercise. ⁴⁴ -Although various cutoffs have been proposed for an abnormal
11	PAWP during exercise, <u>T</u> the multi-point slope of PAWP and cardiac output may prove to be <u>a more</u>
12	reliable measure to discriminate between occult LHD and normal left-sided response to exercise, with >
13	2 mm Hg/L/min being considered abnormal. ⁴⁵ the best discriminator of occult LHD, with > 2 mm
14	Hg/L/min being considered abnormal. It may also be less prone to issues with respiratory swings if all
15	pressures are measured in a consistent manner. ⁴⁶
16	pressures are measured in a consistent manner. ⁴⁶
17	Therapeutic strategies
18	The significant gaps in understanding the complex pathobiology processes and comorbidities
19	that complicate or drive the development and progression of PH has rendered the search for effective
20	therapies particularly difficult. Furthermore, PH may represent a marker of disease severity rather than
21	an optimal target for therapy. Select clinical trials with biologic plausibility to treat PH-HFpEF are
22	summarized in TABLE 2. Currently, there are no pharmacologic agents that are approved to specifically
23	target PH in the setting of HFpEF, a result of disappointing results from these numerous studies. Loop

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1	diuretics for relief of volume overload and concomitant treatment of co-morbidities are the mainstays of
2	therapy in HFpEF, and therefore, PH-HFpEF. In addition to normalization of intracardiac and pulmonary
3	pressures and symptom relief, diuresis associated increases in PAC reduce pulsatile loading to the RV.
4	The use of pulmonary artery monitoring devices may be particularly useful to achieve and maintain
5	euvolemia. The CHAMPION trial was a prospective randomized control trial that enrolled 550 patients
6	with heart failure with both reduced and preserved ejection fraction. Subjects randomized to
7	hemodynamic guided care had substantially more medication titrations (principally diuretics) and
8	experienced a significant reduction in heart failure hospitalizations compared to controls. For one of the
9	first times, subjects with HFpEF and HFrEF showed similar benefit. ⁴⁷ Post-marketing surveillance study of
10	more than 2000 patients (34% PH-HFpEF) yielded similar results. ⁴⁸
11	The role of mineralocorticoid receptor antagonist spironolactone in HFpEF was studied in the
12	TOPCAT trial. ⁴⁹ Although the trial failed to meet its primary endpoint, perhaps due to enrollment
13	irregularities in Russia and Georgia, a reduction in HF hospitalizations were noted. ⁵⁰ Animal and
14	preliminary human data in PAH suggest that aldosterone antagonists may reduce pulmonary
15	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
16	
17	is unknown. In addition, a large cohort of veterans with pulmonary hypertension suggested a mortality
18	benefit with ace inhibitors and angiotensin-receptor blockade. This included veterans with left heart
19	disease; however, HFpEF was not specifically differentiated in this cohort. ⁵²
20	In addition to the optimization of filling pressures, management of the underlying comorbidities
21	like AF, coronary artery disease, systemic hypertension, and metabolic syndrome, and diabetes mellitus
22	is necessary. These factors are prognostically relevant and may be associated with unique and
23	targetable phenotypes. ^{53,54} The presence of underlying valvular heart disease should be investigated and
24	considered as potential therapeutic targets. AF is highly comorbid with HFpEF, with the combination
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3 4	1	often exacerbating the likelihood of hospitalization. Rhythm control strategies including catheter
5 6	2	ablation may offer benefit over rate control, though data from a prospective, randomized control trial is
7 8 9	3	needed. ⁵⁵ With the increasing prevalence of an obesity/metabolic HFpEF phenotype, weight loss
9 10 11	4	management, and aerobic exercise are critical interventions and have both been shown to improve
12 13	5	exercise tolerance and reduce body weight in HFpEF. ⁵⁶
14 15 16 17	6	
18 19	7	PAH targeted therapies
20 21 22	8	Studies of pulmonary vasodilators in PH-HFpEF have largely been disappointing. Although
23 24	9	phosphodiesterase-5 (PDE5) inhibitors have proven efficacious in PAH, their role in PH-HFpEF remains
25 26 27	10	unproven. In a prospective placebo-controlled single-center trial of 44 patients with PH-HFpEF defined
27 28 29	11	by elevated pulmonary artery systolic pressure of (PASP) > 40 mm Hg and severe right ventricular
30 31	12	dysfunction, sildenafil use compared to placebo showed improvement in pulmonary pressures, RV
32 33	13	function and RV dimensions at 6 months. ⁵⁷ Though it was not enriched for CpcPH, the RELAX study of
34 35 36	14	sildenafil use in subjects with HFpEF did not improve mean pulmonary artery pressure, PAWP, CO,
37 38	15	exercise tolerance or VO2. ^{58,59} In a post hoc analysis of the trial, sildenafil also failed to reduce RV
39 40	16	afterload. ⁶⁰ Similar results were obtained in other studies of sildenafil in predominately IpcPH. ⁵⁸ In a
41 42 43	17	randomized double-blind placebo-controlled trial of 222 patients (108 patients with CpcPH and 80 IpcPH
43 44 45	18	patients isolated post-capillary) with pulmonary hypertension and PHHFpEF related to successfully
46 47	19	corrected (at least 1 year before enrollment) valvular heart <u>disease</u> , sildenafil treatment was associated
48 49 50	20 21	with worse clinical outcomes compared to placebo. ⁶¹ The PASSION trial evaluating the effects of tadalafil
50 51 52	21	on HFpEF and CpcPH is currently underway.
53 54	22	While PDE5 inhibitors have failed to show benefit in undifferentiated PH-HFpEF and remain under
55 56 57 58 59	23	investigation in CpcPH, another class of medications affecting the same downstream signaling pathways

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	1	has also been evaluated. Whereas PDE5 inhibitors prevent the breakdown of cGMP – a vasodilatory and
	2	antiproliferative molecular signal — the soluble guanylyl cyclase stimulators (sGC stimulators) function
I	3	to directly increase sGC levels in the vasculature and other tissues. DILATE-1 trial evaluated the role of
	4	the sGC stimulator riociguat compared to placebo in 39 patients with PH-HFpEF and notably included 5
	5	patients with CpcPH. No significant change in mPAP or PVR at 6 hours was noted in this proof-of-
	6	concept study. Subsequent, large prospective randomized trials of sGC-stimulators have shown no
	7	benefit in enrolled, undifferentiated HFpEF subjects. ⁶²⁻⁶⁴ Finally, several investigations targeting the
	8	antagonism of endothelin pathway have been reportedtype A receptors has been undertaken, with
	9	consideration for the potential to reduce pulmonary vasoconstriction. A study of the selective
1	.0	endothelin type A (ET _A) receptor sitaxsentan in 192 HFpEF subjects with HFpEF did not meet statistical
1	.1	significance for end points including New York Heart Association (NYHA) functional class, heart failureHF
1	2	hospitalizations-stays, measures of diastolic function, or quality of life questionnaire scores. However,
1	.3	there was a significant increase in exercise tolerance (median treadmill time)65 - Subsequent study of
1	.4	endothelin receptor antagonism in tThe MELODY-1 evaluated the acute role of the endothelin receptor
1	.5	antagonist macitentan in patients with CpcPH identified by diastolic pressure gradient ≥-7 <u>mmHg</u> and
1	.6	PVR \geq 3WU. The trial was powered to evaluate safety endpoints. At 12 weeks, more adverse events
1	.7	were noted with \underline{m} acitentan compared to placebo with no improvement in PVR or mean right atrial
1	.8	pressure. ^{_66} _ <u>Unfortunately, Ithe SERENADE trial, which specifically enrolled patients with HFpEF and</u>
1	.9	pulmonary vascular disease or RV dysfunction, also aimed to test macitentan, but was stopped
2	20	prematurely (NCT03153111). – At present, PAH-specific therapies should be avoided in PH-HFpEF. ³⁷ This
2	1	recognition is relevant given relatively recent real-world evidence suggesting that PAH specific therapies
2	2	may be prescribed nearly as frequently for PH-LHD as PAH and argues that these therapies are used
2	3	more frequently than might be assumed for PH-LHD in the rare setting of complex and multifactorial
2	4	etiologies. ⁶⁷

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1		19
2 3 4	1	
- 5 6 7	2	Early phase or investigational therapies
8 9	3	Several on-going pharmacologic and device therapies are being studied in PH-HFpEF. Early
10 11	4	phase studies of <u>intra-</u> atrial <u>septal</u> shunt devices <u>(IASD)</u> have shown promise in exercise-induced HFpEF
12 13 14	5	but have not specifically enrolled patients with PH-HFpEF. ^{_68,69} In early studies, The use of IASD has been
15 16	6	shown to bewere associated with sustained reduction in PVR, pulmonary Ea and improvement in
17 18 10	7	pulmonary arterial compliance (PAC) atthat extends out to 6 months ⁶⁹ In an open-label study, the use
19 20 21	8	of IASD was associated with sustained improvements in New York Heart Association NYHA functional
22 23	9	class (P <0.001), quality of life (P < 0.001) and 6- minute walk distance (P < 0.01)70 Whether those with
24 25	10	CpcPH may be at higher risk of RV dilation or dysfunction after these therapies remain unknownIn a
26 27	11	study of 37 patients with group 2 PH with HF with EF of at least 40%, New York Heart Association NYHA II
28 29 30	12	or III heart failure, once weekly Levosimendan compared to placebo showed did not significantly reduce
31 32	13	the primary endpoint of exercisePAWP (-1.4 mmHg, 95% Cl [-7.8، 4.8],-p=0.65). However,
33 34	14	Levosimendan reduced PAWP measured across all exercise stages (-3.9±2.0 mmHg, p=0.047), and
35 36	15	resulted in a 29.3 meter (95% CI [2.5, 56.1], p=0.033) improvement in 6 minute walk distance compared
37 38 39	16	to placebo. ⁷¹ Metformin is currently being studied in a phase II trial for PH-HFpEF (NCT03629340) based
40 41	17	upon several lines of evidence including improved heart failure outcomes in patients with type 2
42 43	18	diabetes in several large observational cohorts, decrease in cardiac work associated with reduced
44 45	19	myocardial glucose uptake and fatty acid oxidation, and improvements metabolism in both skeletal
46 47 48	20	muscle and pulmonary vascular smooth muscle via upregulation of the SIRT3-AMPK-Glut4 pathway. ⁷²
49 50	21	In keeping with the metabolic mechanisms contributing to HFpEF, two large, randomized trials
51 52	22	(EMPEROR-Preserved - NCT03057951; DELIVER - NCT03619213) are evaluating the role of SGLT2
53 54 55	23	inhibitors in HFpEF; results of which could inform the management of PH-HFpEF. ⁷²
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1	Nitrite, which is reduced to nitric oxide by hemoglobin, is currently being studied in an oral
2	formulation for PH-HFpEF (NCT03015402), having shown promise in an inhaled formulation in PH-HFpEF
3	predominately through improvement in PAC. However, a broader study in HFpEF (uncontrolled for PH)
4	did not show improvement in exercise capacity as assessed by CPET and 6-minute walk distance. ⁷³
5	Early-phase studies of oral milrinone have also been conducted suggesting improvement in exercise
6	hemodynamics and improved quality of life measures74 Finally, PA denervation therapy in CpcPH was
7	studied in the PADN-5 study, which included approximately $4\underline{0}\theta$ % of subjects with HFpEF. Compared
8	with sildenafil alone, PA denervation resulted in a significant increase in 6-min walk and lower PVR. ⁷⁵
9	Additional studies of this potentially promising therapy, such as TROPHY-II (NCT03611270) are
10	underway.
11	
12	underway. Conclusion:
13	In HFpEF, the development of pulmonary hypertension is recognized as an important
14	contributor to morbidity and mortality. Differentiation from PAH can be subtle and requires careful
15	attention during diagnostic evaluation. Recent studies have paved the way for a better understanding
16	of the pathobiology and relevant diagnostic and prognostic methodologies. Those therapeutic
17	interventions aimed at targeting elevated pulmonary pressures have largely been disappointing but
18	novel therapeutic strategies are currently being studied.
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1	Figure Legend
2	Figure. Hemodynamic assessment of pulmonary hypertension (PH) due to heart failure with preserved
3	ejection fraction (HFpEF). RV: right ventricular; RHC: right heart catheterization; LHD: left heart disease;
4	PAWP: pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure; CTEPH:
5	chronic thromboembolic PH. a) Pre-test probability of PH-LHD is based on the features presented in
6	table 1. RHC is recommended in intermediate probability when risk factors of pulmonary arterial
7	hypertension/CTEPH are present and/or if there is evidence of right ventricle abnormality. If the
8	probability is high, patients should be managed according to recommendations for LHD. b) For the
9	assessment of PH, RHC should be performed at expert centrescenters. In patients with
10	intermediate/high probability (table 1) and PAWP between 13 and 15 mmHg, PH-HFpEF is not excluded;
11	provocative testing (tables 2 and 3) should be considered. #: for patients with systemic sclerosis, risk
12	factors for CTEPH and/or unexplained dyspnea; [¶] : after [2]; ⁺ : if PAWP >15 mmHg, LVEDP validation
13	should be considered. Reproduced with permission of the ${ m C}$ ERS 2021: European Respiratory
14	Journal 53 (1) 1801897; DOI: 10.1183/13993003.01897-2018 Published 24 January 2019. ⁴¹

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Table 4 Due to struct a little	a flaft has ant all a same (LLID) where a	to an electronic sector in the sector of the	ender and a second s
Lable 1 Pre-test probabili	y of left heart disease (LHD) pheno	ntvne versus Plilmonarv arterial r	ivpertension or pre-capillary PH
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>70 years	60–70 years	<60 years
>2 factors	1–2 factors	None
Yes	No	No
Current	Paroxysmal	No
Present	No	No
LBBB or LVH	Mild LVH	Normal or signs of RV strain
LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; <i>E/e</i> ′ <13
Mildly elevated V'_{E}/V'_{CO2} slope;	Eleveted V'_{i}/V'_{i} eleve or EQV	
		High V'_{E}/V'_{CO2} slope; no EOV No left heart abnormalities
	Yes Current Present LBBB or LVH LA dilation; grade >2 mitral flow elevated V'E/V'CO2 slope; EOV LA strain or LA/RA >1	Yes No Current Paroxysmal Present No LBBB or LVH Mild LVH LA dilation; grade >2 mitral flow No LA dilation; grade <2 mitral flow

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

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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 <i>Circulation 2011</i>	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 <i>JAMA 2013</i> (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 (<i>primary</i>)	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) (<i>p</i> =0.90) at 24 weeks
Abraham et al <i>Circ HF 2014</i> (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 (<i>P</i> <0.0001)
Bonderman et al <i>CHEST 2014</i> (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 <i>NEJM 2015</i> (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	<u>N=28; 15</u> <u>minutes after</u> <u>drug</u> <u>administration</u>	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.

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	exchange 15 min. after administration					
<u>Simon et al</u> JCI Insight 2016	<u>Aerosolized sodium</u> <u>nitrite</u>	<u>N=36; 15-60</u> <u>minutes</u>	WHO group I, II, and III PH. Exploratory for Group 2 PH (PH- HFpEF), change in PVR for Group <u>1 and Group 3</u> 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.
<u>Borlaug et al</u> <u>Circ Res 2016</u>	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 <i>Eur Respir J 2017</i> (MELODY-1)	Macitentan vs. placebo	N = 63, median treatment duration of 12 vs 12.1 weeks in macitentan vs. placebo groups	- LVEF \geq vs. < 50% (stratified by LVEF) and CpcPH confirmed by RHC with mPAP >25 mmHg, PAWP >15 mmHg, and < 25 mmHg, and PVR at rest \geq 3 WU with DPG \geq 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 <i>Eur Heart J 2017</i> (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 LA at 12 weeks vs. placebo, associated with improved QOL
Reddy et al <i>Circ Res 2019</i>	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 \pm 0.5 vs. +0.1 \pm 0.7 WU (<i>p</i> =0.003).

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(Albuterol in		hemodynamic	PCWP ≥15 or	parallel-group,	exercise PCWP,	Albuterol also improved PA
HFpEF)		exercise-	exercise PCWP	placebo-	other measures	compliance, arterial
		testing	≥ 25 mmHg at	controlled trial	of RV reserve	elastance, RV-PA coupling,
		N-700.04	20 W workload	Dhasa Oh	Dhusiaal	and cardiac output
Armstrong et al IAMA 2020	Vericiguat, up-titrated to 15-mg (n = 264) or	N=789, 24 weeks	LVEF ≥ 45%, NYHA class II-III,	Phase 2b randomized,	Physical limitation score	Vericiguat: No improvement of PLS of KCCQ compared
VITALITY-HFpEF)	10 - mg (n = 263) daily	WEEKS	within 6 months	double-blind,	(PLS) of the	with placebo; no change in 6
	oral dosages,		of a recent	placebo-	Kansas City	minute walk distance
	compared with		decompensation,	controlled,	Cardiomyopathy	
	placebo (n = 262) and		and elevated	multicenter trial	Questionnaire	
	randomized 1:1:1.		natriuretic		(KCCQ).	
			peptides			
Jdelson et al	40 mg of praliciguat	N=196, 12	LVEF ≥ 40%,	Randomized,	Change from	Praliciguat: No difference in
IAMA 2020	daily or placebo	weeks	impaired peak	double-blind,	baseline in peak	peak VO_2 or 6-minute walk
			V_{O_2} , and at least	placebo-	V ₀₂ in patients	distance
HFpEF)			2 conditions associated with	controlled,	who completed at least 8 weeks	
			NO deficiency	phase 2 trial.	of assigned	
			NO denoiency		dosing	