Published in final edited form as:

Circulation. 2022 August 16; 146(7): e73–e88. doi:10.1161/CIR.0000000000001079.

Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: A Call to Action:

A Scientific Statement From the American Heart Association

Evan L Brittain, MD, MSc, FAHA [Chair],

Thenappan Thenappan, MD [Co-Chair],

Jessica H Huston, MD,

Vineet Agrawal, MD, PhD,

Yen-Chun Lai, PhD,

Debra Dixon, MD, MS,

John J Ryan, MD, FAHA,

Eldrin F Lewis, MD, MPH,

Margaret M Redfield, MD,

Sanjiv J Shah, MD, FAHA,

Bradley A Maron, MD

American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Lifestyle and Cardiometabolic Health, and Stroke Council

Abstract

This statement focuses on the need to better understand the epidemiology, pathophysiology, and treatment of pulmonary hypertension (PH) in patients with heart failure with preserved ejection fraction. This clinical phenotype is important because it is common, strongly associated with adverse outcomes, and lacks evidence-based therapies. Our goal is to clarify key knowledge gaps around PH due to HF with preserved ejection fraction and to suggest specific, actionable scientific directions for addressing such gaps. Areas in need of additional investigation include refined disease definitions and interpretation of hemodynamics as well as greater insights on non-cardiac contributors to PH risk, optimized animal models, and further molecular studies in patients with combined pre- and post-capillary PH. We highlight translational approaches that may provide important biologic insight into pathophysiology and reveal new therapeutic targets. Finally, we discuss the current and future landscape of potential therapies for patients with heart failure with preserved ejection fraction and pulmonary vascular dysfunction including considerations of precision medicine, novel trial design, and device-based therapies among other considerations. This statement provides a synthesis of important knowledge gaps culminating in a collection of specific research priorities that we argue warrant investment from the scientific community.

Introduction and Call to Action

Heart failure with preserved ejection fraction (HFpEF) is one of the leading causes of pulmonary hypertension (PH) in the world.[1] The development of PH and particularly pulmonary vascular disease (which distinguishes functional pressure elevation from vascular dysfunction or remodeling) are among the strongest risk factors for adverse outcomes in HFpEF.[2] Despite this recognition, no evidence-based therapies exist for PH due to HFpEF (PH-HFpEF), in part because the pathophysiology is poorly understood. In this call to action we encourage the scientific community to prioritize the study of PH-HFpEF, which has implications for collaboration, data sharing, and clinical trial design, among other considerations. The goal of this statement is to clarify key knowledge gaps around PH-HFpEF and to suggest scientific directions for addressing such gaps, which we synthesize in Table 1.

PH-HFpEF Definition, Prevalence, and Incidence

The definition of HFpEF varies widely between societal statements, guidelines, and clinical trials. Equally varied is the PH-HFpEF definition, which is often based on echocardiographic data rather than the gold standard, right heart catheterization (RHC). [3–5] The current consensus definition of different PH hemodynamic profiles is shown in Table 2 along with alternative definitions used in clinical trials and epidemiologic studies. Most data on HFpEF prevalence is derived from registries and electronic health record (EHR)-based studies. Consequently, important details on PH subgroups are unavailable or potentially inaccurate, since these sources rely primarily on international classification of disease codes and are associated with selection bias towards tertiary referral populations.[15, 16] The fact that most patients with HFpEF are not referred for RHC also likely introduces bias in retrospective cohorts with invasive hemodynamics including potential enrichment with patients more challenging to manage. Invasive phenotyping of patients with suspected HF and/or PH is important because individuals with mean PA pressure (mPAP) ≥19 mmHg as well as those with mildly elevated pulmonary pressure and pulmonary vascular resistance (PVR) ≥2.2 WU are at particularly elevated mortality risk.[17]

The reported prevalence of PH-HFpEF varies widely depending on the population (clinical trial participants vs. hospital-based cohorts), diagnostic approach (echocardiography or RHC) and the definition used (Table 3). For example, the prevalence of a tricuspid regurgitant velocity >2.9m/sec was 36% among TOPCAT echocardiography sub-study participants whereas the prevalence was 83% in a population-based cohort using a similar definition.[2, 20] Notably TOPCAT was not powered specifically to assess PH-HFpEF and, thus, suboptimal for guiding information on prevalence. Longitudinal data on PH incidence and progression among well-phenotyped PH-HFpEF cohorts are also lacking.

Diagnosis of PH-HFpEF and Interpretation of Hemodynamic Data

In patients with suspected PH-HFpEF, RHC usually reveals PH, elevated pulmonary artery wedge pressure (PAWP), and normal or elevated PVR. However, in some cases, PH may be present without significant elevation of PAWP (often in the setting of

diuretic therapy). Provocative maneuvers with exercise or fluid challenge can unmask left ventricular (LV) diastolic dysfunction.[23] These maneuvers may improve diagnostic accuracy but suffer from lack of widespread feasibility and standardization and variability in interpretation. Practical limitations to the widespread use of provocative maneuvers include equipment constraints as well as the absence of standardized patient selection criteria or evidence-based guidelines informing the interpretation of test results.[24, 25] Patient positioning in invasive cardiopulmonary exercise testing (CPET) varies between upright, supine, and semi-recumbent by center, as does workload protocol and even PH-HFpEF hemodynamic definitions (ie mPAP/cardiac output slope versus standard hemodynamic variables).[12, 26] Fluid challenge may be simpler than exercise but criteria for PH-HFpEF diagnosis, association of fluid-challenge hemodynamics with outcomes, and implications for management remain to be defined.

When PH patients have a low resting PAWP that subsequently increases with provocation, they are generally categorized as PH-HFpEF or PH with “occult left heart disease.” It remains unclear if these patients are simply adequately diuresed or the resting PAWP are persistently low and they develop hemodynamic congestion primarily with exercise or other provocation. Interpretation of provocative maneuvers must incorporate pre-test probability of disease, an important factor which can be difficult to standardize.

There is a critical need for a non-invasive tool to fully characterize the presence of pulmonary vascular dysfunction, right ventricular (RV)-PA coupling, and intracardiac filling pressures in HFpEF. An ideal tool would differentiate HFpEF patients without PH from those with isolated post-capillary PH (Ipc-PH) versus combined pre- and post-capillary PH (Cpc-PH) non-invasively. One such measure may be non-invasive assessment of RV-PA coupling [tricuspid annular plane systolic excursion/PA systolic pressures (PASP)] which is associated with increased mortality risk, even when the estimated PASP is near normal.[27] Careful echocardiographic assessment of RV-PA coupling, estimated PVR, PA acceleration time, or composites of echocardiographic features may help stratify risk in PH-HFpEF patients and drive further testing. However, echocardiography, while widely available and non-invasive, has significant limitations beyond image quality. Two-dimensional echocardiography does not characterize the crescentic anatomy of the RV fully or reliably quantify right atrial pressure, and is associated with limited accuracy for estimating PASP at peak exercise. [28] Although 3-D echocardiography may offset some of these limitations, it is not widely used in mainstream clinical practice.[29, 30] Cardiac MRI (CMR) provides reliable and reproducible functional and volume assessment of the RV and ventricular-arterial coupling which is important in prognostication.[31, 32] Beyond RV assessment, left atrial volume and septal angle by CMR (or cardiac CT) can help differentiate between PH-HFpEF from PAH.[33–35] Nevertheless, diagnosing and prognosticating PH patients appropriately requires invasive testing since at present key hemodynamic parameters including PAWP, PVR, and cardiac output are not valid measures using non-invasive imaging tools. Provocative maneuvers during echocardiography may influence the pre-test probability of PH on RHC and provide insight the into disease, particularly under circumstances in which valvular disease or left ventricular (LV) dysfunction are observed.

Non-Cardiac Contributors to PH Risk in HFpEF

The specific effects of age, sex, race, and comorbid conditions on PH risk in patients with HFpEF requires further study. Female sex and Black race were risk factors for PH in unselected cohorts referred for diagnostic testing, but it is unclear if this is driven by treatment differences and/or socioeconomic status.[36, 37] Systematically collected data examining potential influences of other comorbidities (e.g. sleep disordered breathing, atrial arrhythmias, and lung disease) on PH risk or outcomes in HFpEF is lacking. There is evidence that obesity alone increases PA pressure (but not pulmonary vascular remodeling).[38] Obesity and metabolic syndrome co-exist in up to 50% of patients with PH due to left heart disease (PH-LHD) with some data suggesting that the metabolic syndrome and the associated inflammatory milieu may contribute to pulmonary vascular disease.[39, 40]. Sleep-related breathing disorders are common in PH-HFpEF and suspected to contribute to PH via intermittent hypoxia with resultant cytokine and hormonal derangements that lead to pulmonary vascular remodeling.[41] Implementation of positive airway pressure therapy is associated with a reduction mPAP and PVR, though a direct link pathophysiologic link between sleep-disordered breathing in pulmonary vascular disease *per se* has not been established.[42, 43] More complete understanding of the interaction between obesity and PH is critical as the obese-HFpEF phenotype is so common and likely, pathophysiologically distinct.[44]

Cancer and cancer therapies are associated with increased risk of cardiovascular disease, including HFpEF, through effects on diastolic and microvascular dysfunction among other mechanisms.[45, 46] The potential downstream effects of these interactions on pulmonary pressure are unknown. Moreover, cancer therapies (most notably the tyroskine kinase inhitibor dasatinib) may also cause direct pulmonary vascular dysfunction.[47] These observations highlight the need for clinical and epidemiologic vigiliance with respect to PH-HFpEF risk as new cancer therapeutics emerge and cancer-related cardiovascular surveillance becomes standard-of-care.

Combined Pre-and Post-Capillary PH: Diagnosis and Pathophysiology

Combined pre-and post-capillary PH differs from Ipc-PH by the presence of PVR ≥3WU. The prevalence of Cpc-PH among retrospective heart failure referral populations ranges from 12–40%.[18, 37, 48, 49] It is important to distinguish Cpc-PH from Ipc-PH as Cpc-PH is associated with worse outcomes and, in contrast to Ipc-PH, is a population currently enrolling in targeted clinical trials testing therapies for pulmonary vascular disease.[18, 37] The hemodynamic definition of Cpc-PH has varied over time and should be standardized to facilitate clinical trials as different therapeutic approaches for Cpc-PH and Ipc-PH may be needed.[37]

The pathophysiology underlying the Cpc-PH subgroup is poorly understood. Chronic, severe left atrial hypertension and left atrial dysfunction leading to vascular remodeling is typically cited as the primary driver of Cpc-PH, a notion based on observations described in patients with rheumatic mitral valve stenosis. However, this fixed obstructive model is dissimilar to the dynamic changes in congestion and loading that are seen with PH-HFpEF. Varying

theories exist about the development of Cpc-PH in HFpEF. While generally regarded as pathologic, it is possible that pulmonary vascular changes in HFpEF may be adaptive, specifically working to protect the left heart from intolerable preload. [50] Conversely, Cpc-PH may reflect maladaptive progression of Ipc-PH driven by persistent, severe hemodynamic congestion, or represent an intermediate hemodynamic pathophenotype with similarities to PAH. Venous remodeling occurs in Cpc-PH, potentially representing a subgroup of patients that develop disease akin to a pulmonary veno-occlusive *forme fruste* than PAH *per se*. There may be subtypes of Cpc-PH influenced by genetic variants or other molecular drivers that predispose individuals with left atrial hypertension to the development of pulmonary vascular disease. Single nucleotide polymorphisms shared by Cpc-PH and PAH have been identified, although the generalizability of these variants to other Cpc-PH cohorts is not known.[37] Acquired metabolic dysfunction (e.g. obesity, insulin resistance) may also increase risk of developing vascular remodeling in patients with PH-HFpEF. Worsening of the obesity epidemic would predict a rising prevalence of Cpc-PH. It is also possible that many patients with Ipc-PH at the time of diagnosis progress to Cpc-PH over time, though longitudinal data are lacking.

Pathophysiology of PH and Translational Approaches to Understand Vascular Remodeling in HFpEF

Little is known about pathophysiological processes and cellular/molecular mechanisms involved in the regulation of PH-HFpEF. What little we do know suggests that pulmonary vascular pathology in PH-HFpEF is multifactorial and involves complex systemic alterations. PH-HFpEF patients display global (veins, indeterminate vessels, and arteries) pulmonary vascular remodeling and the severity of PH correlates most strongly with intimal thickening in pulmonary veins and small indeterminate vessels.[51] Of note, only a subset of HFpEF patients display more than 50% of venous intimal thickening, indicating that individual patients who develop the disease can vary markedly. These structural changes are observed regardless of LV systolic function but appear particularly striking in HFpEF. Lymphatic function and drainage are impaired in obesity, metabolic syndrome, and chronic inflammatory states, all recognized co-morbidities of HFpEF. There is emerging evidence of reduced lymphatic reserve in HFpEF which may play a role in PH-HFpEF and the impact on cardiac function and outcomes.[52]

The role of right ventricular (RV) pathology and emerging evidence for unique RV pathophenotypes also warrants further study. For example, in patients with HFpEF and Cpc-PH, exercise can unmask impaired RV systolic reserve and enhanced interventricular interdependence that may not be evident at rest.[53] Longitudinal studies of RV structure and function are a priority for further study based on evidence that the RV may decline out of proportion to changes in LV structure and function in patients with HFpEF.[54] Recent data also suggest a potential contribution of atrial myopathy due to atrial fibrillation in promoting pulmonary vascular disease and RV dysfunction in patients with HFpEF.[55] Whether atrial fibrillation management (i.e. rhythm vs rate control) affects the natural history of PH and RV function is unknown.

Knowledge of pulmonary vascular structure is critical but histology is limited to research lung biopsies in HF patients undergoing thoracic surgery or post-mortem sampling.[51] With advances in proteomics, transcriptomics, and digital spatial profiling in formalin fixed paraffin embedded samples, autopsy specimens now provide a means to study not only histopathology of PH-HFpEF but also molecular mechanisms.[51] Innovative imaging solutions for assessing global pulmonary vascular structure are needed.

A significant shortcoming of PH-HFpEF research is the lack of human HF pulmonary vascular tissue to characterize molecular mechanisms. Culture and molecular profiling of PA endothelial cells from the catheter balloon tip[56] and related approaches[57] are underway and may provide a new avenue for characterizing the PA endothelial cell response to stressors or potential therapies. Molecular profiling of transpulmonary blood samples may lead to diagnostic tools to distinguish Ipc-PH and Cpc-PH and facilitate systems biology and -omics approaches to the pathophysiologic mechanisms driving pulmonary vascular remodeling.[58,59] The growing expansion of large de-identified databases with associated biobanks offers an important avenue of investigation to understand how genetic variation and plasma markers associate with PH-HFpEF risk.[58, 60] These resources will be important adjuncts to mechanistic basic studies in animal models to verify or support causal pathways in the development of pulmonary vascular remodeling in HFpEF.

Animal Models of PH-HFpEF

Given the heterogeneity of disease phenotypes and diverse cardiac/non-cardiac contributing factors, relevant and reliable animal models need to be selected carefully as many models may only resemble a certain subtype of PH-HFpEF patients (Table 4). For example, single-hit aortic banding animal models may be useful for examining the contributions of cardiac factors without interference from additional comorbidities.[61] Leptin-deficient (ob/ob) mice and high-fat diet (HFD)-exposed mice have been used to model metabolic syndrome-associated PH and/or HFpEF.[62] The administration of HFD in a mouse prone to development of metabolic syndrome, the AKR/J mouse, recapitulates many features of PH-HFpEF, including a unique obese HFpEF-related RV phenotype seen in human HFpEF.[63] Note that not all mouse strains develop HFD-induced PH-HFpEF and the disease phenotype is mild in susceptible strains.[64]

Two promising multi-hit rat models of PH-HFpEF have been developed recently based on the obesity/metabolic phenotype, comorbidities, pulmonary vasculopathy and/or inflammation (Table 4). The supra-coronary aortic banding together with HFD and olanzapine (an antipsychotic associated with insulin resistance) model appears to recapitulate many of the key features of human disease, although exercise intolerance, kidney dysfunction and skeletal muscle abnormalities have not been reported.[65] The combination of SU5416 (vascular endothelial growth factor receptor-type A inhibitor known to induce lung endothelial injury and apoptosis) in obese ZSF1 rat represents a reproducible model that recapitulates the combination of systemic alterations, comorbidities, physical inactivity and exercise intolerance often found in human PH-HFpEF.[66] Notably, SU5416-treated obese ZSF1 rats develop exercise-induced PH (EIPH) during treadmill exercise.[67] As approximately 50–88% of HFpEF patients develop EIPH, even at low-level exercise, this

model may serve as an important tool for exploring potential mechanisms and treatment options for EIPH in HFpEF.[14]

Finally, there is an unmet need to develop and use large animal models, which more closely model human physiology and thus may offer more relevant pathophysiologic insights. The use of pulmonary vein banding recapitulates the severe pulmonary arterial, pulmonary venous, and right ventricular remodeling that has been observed in HFpEF patients (Table 4).[51, 68] The search for an ideal animal model that fits all aspects of the disease remains challenging due to phenotypic heterogeneity and the multifactorial nature of the disease. Through careful definition of specific questions, selection of appropriate fit-for-purpose models (preferably more than one) and comprehensive characterization of multidimensional phenotypical readouts, useful clinical insights may be obtained.

Treatment Approaches

The management of PH-HFpEF is challenging because of the lack of proven PH therapies in the setting of HFpEF. Conventional practice in treating secondary PH is to focus initial efforts on treating the underlying condition. Questions regarding treatment approaches include (1) Is PH simply a marker of disease severity or truly a target for therapy in PH-HFpEF? (2) Should Cpc-PH be considered separately from Ipc-PH in clinical trials? and (3) Should greater consideration be given to the role of RV dysfunction in HFpEF?

Limitations of prior PH-HFpEF studies

To date, randomized controlled trials (RCTs) of PH therapies in left heart disease have included both HFpEF and heart failure with reduced ejection fraction (HFrEF) patients, varied in method of diagnosis of PH, or applied varied definitions of PH making it more difficult to determine therapeutic response. Among HFpEF RCTs (Table 5), prospective evaluation for PH has been rare, which limits the interpretation of trial results with respect to PH responsiveness. Important challenges to the prospective evaluation of PH include (among others) the feasibility of RHC for all study participants and the reliability and reproducibility of non-invasive diagnostic criteria. Previously completed and ongoing phase 3 RCTs in HFpEF vary in phenotyping patients, ranging from simple clinical and biomarker phenotyping (e.g., EMPEROR-Preserved [SGLT2 inhibitors]) to Doppler echocardiography in a subset (e.g., PARAGON [sacubitril/valsartan]) to RHC with exercise in all participants (e.g., REDUCE LAP-HF II [interatrial shunt device]).[73–75] Development of a non-invasive diagnostic score that could reasonably differentiate Cpc-PH from Ipc-PH would be valuable. A validated non-invasive score would circumvent the limitation that invasive hemodynamic testing can impose on large, multi-site studies, particularly in resource-limited areas.

Precision therapeutics and novel trial designs

The heterogeneity of the HFpEF syndrome is a prevailing reason for the disappointing track record of many prior RCTs, and has sparked calls for a phenotype-specific approach to HFpEF with precision medicine trials that tailor specific therapies to specific HFpEF subphenotypes such as PH-HFpEF.[76]

Novel methods to identify patients with PH-HFpEF may improve efforts to target the specific PH subphenotypes and make trial enrollment more efficient. For example, machine learning using electronic health record data and/or electrocardiograms and echocardiograms have also been developed for the automated identification of patients with specific types of myocardial disease and could be applied to PH-HFpEF as well to identify patients in a high-throughput fashion.[75, 77–80]

Successful RCTs in PH-HFpEF will likely require novel RCT designs. Examples include umbrella trials, bucket trials, and adaptive trials.[81] An umbrella design would involve taking the heterogeneous group of HFpEF patients and performing phenotyping (e.g., biomarkers, echocardiography, invasive hemodynamics, exercise testing) and identifying more homogeneous subtypes such as Cpc-PH that would then be directed towards targeted RCTs. In this way the RCT is enriched (i.e. enrichment trial) for patients who are most likely to respond to the treatment being tested, which is an approach that has been used in multiple PH-HFpEF trials (Table 5). Bucket trials involve identifying patients who share a similar disease mechanism that could be ameliorated by the treatment being tested. For example, patients with Group 1, Group 2 (including PH-HFpEF), and Group 3 PH could be tested for a specific genetic variant or other molecular marker associated with pulmonary vascular remodeling; if present, they would then be enrolled in an RCT for a medication that specifically targets the molecular mechanism associated with that genetic variant. A similar approach could be used across all types of PH for drugs or devices that treat RV dysfunction. In these trials, the various types of disease that enter the bucket trial could have a unified outcome or varied outcome depending on the type of disease. Finally, in adaptive trials, pre-specified rules are incorporated to account for early information from intermediate endpoints, thereby increasing likelihood for success (by enhancing potential efficacy by homing in on the type of patient most likely to benefit, improving safety, or picking the best outcome that will most likely show a benefit). Additionally, defining appropriate clinical trial endpoints is important for the successful identification of therapeutic interventions. Primary endpoints for PH-HFpEF trials may benefit by learning from both prior HFpEF and PAH trials and utilize a combination of recurrent HF hospitalizations, six minute walk distance, and Kansas City Cardiomyopathy questionnaire (KCCQ) (Table 5).

Mechanistic targets in PH-HFpEF

PH-HFpEF is a multi-factorial syndrome with a range of disease entities (e.g. Ipc-PH, Cpc-PH, and likely others) which creates a conundrum on which disease mechanisms to target. Treatment of HFpEF to avoid progression and development of PH is one approach. Recent large-scale RCTs such as PARAGON-HF and EMPEROR-Preserved may assist with this goal (Table 5).[71, 74] Additional mechanistic targets include pulmonary vasodilation, RV dysfunction, RV metabolism, PA compliance, RV-PA coupling, splanchnic vasodilation, and counteracting the genetic predisposition to maladaptation of the pulmonary vasculature and extracellular components, which lead to pulmonary vascular remodeling.[82–84] For example, inhaled albuterol (beta-agonist) was shown to improve RV-PA coupling, exercise PVR, and left heart filling and therefore may have utility in a PH-HFpEF population.[69] Treatment of pathological changes in the pulmonary veins and treatment of pulmonary endothelial dysfunction represent two additional targets.[51]

Role of patient reported outcomes

The 6th World Symposium on PH highlighted the importance of patient perspectives and patient reported outcomes (PROs), specifically advocating for the inclusion of PROs as secondary endpoints in RCTs.[85] Given that there are no validated surrogate endpoints in PH-HFpEF, assessment of PROs such as quality of life, health status, functional status, or exercise capacity (cardiopulmonary exercise tests or 6MWD) in addition to hospitalizations and mortality is important. There are several validated quality of life measures for use in both PAH and HF with some validated in both populations.[86] Validation and incorporation of quality of life measures with functional measures such as 6MWD may help to identify therapies in PH-HFpEF that substantially improve patient QoL or health status, which are important to patients and predictors of prognosis.

Exercise and potential role of digital health

Supervised exercise programs (e.g. cardiac rehabilitation) are consistently associated with improvement in quality of life and cardiorespiratory fitness in patients with HFpEF or PH.[87–91] However, no data exist on potential role of exercise in patients with PH-HFpEF specifically. Moreover, the mechanisms by which activity interventions improve exercise capacity (e.g. skeletal muscle function, cardiopulmonary reserve, etc.) warrant further study. The widespread use of commercial activity monitors may facilitate remote, unsupervised interventions to increase physical activity. For example, text-based smartphone motivational interventions could be used to augment activity levels in PH-HFpEF as was recently shown to be feasible in a PAH population.[92] Such interventions may be an attractive adjunct to medical care because many patients do not have easy access to rehabilitation facilities and many insurers do not cover costs of supervised exercise programs for HFpEF or PH.

Metabolic interventions

More than half of patients with PH due to left heart disease have metabolic syndrome.[40] Ranchoux and colleagues demonstrated a link between metabolic syndrome and the development of precapillary PH via activation of interlukin-6 (IL-6) associated pathways in animal models as well as increased expression of IL-6 in lung tissue of patients with PH due to left heart disease.[65] Metformin, anti-IL-6 antibodies, or other anti-inflammatory agents along with SGLT2-inhibitors and GLP1-receptor agonists may represent novel therapeutic interventions for the treatment of PH-HFpEF (Table 5).

Repurposing pulmonary vasodilators

The success of pulmonary vasodilator therapy in PAH has led to the investigation of these therapies in PH-HFpEF. Unlike RCTs of these drugs in all HFpEF, subsequent RCTs used a phenotype-specific approach to enrich the trials with patients deemed most likely to benefit (Table 5). Macitentan, an endothelin receptor antagonist, and oral treprostinil, a prostacyclin analogue, were tested in the SERENADE and SOUTHPAW trials, respectively.[93, 94] Each of these trials (1) required a PH-HFpEF phenotype with either elevated PVR or RV dysfunction; and (2) incorporated a run-in phase to select out those with fluid retention or pulmonary edema. Both trials were terminated early for slow enrollment, the Achilles heel of precision medicine trials. Despite the desire to utilize and study pulmonary vasodilators in

PH-HFpEF, given the poor track record of these drugs thus far, current guidelines/consensus statement strongly recommend against using Group 1 PH therapies in PH due to left heart disease outside of a clinical trial setting for HFpEF and Cpc-PH (30545974).

Augmenting RV function as a therapeutic target

The HELP-PH-HFpEF trial used a similar approach to SERENADE and SOUTHPAW but enrolled patients with invasive hemodynamic evidence of PH-HFpEF and also included a 24-hour run-in phase of intravenous levosimendan (a calcium sensitizer that has inotropic effects) to determine whether the drug reduced exercise PAWP by > 4 mmHg, which was required for subsequent randomization to levosimendan vs. placebo.[93–95] Although it did not meet its primary endpoint of lowering exercise PAWP, levosimendan was associated with a 30-meter placebo-corrected increase in 6MWD, and had favorable hemodynamic effects, thereby supporting the novel trial design as a potential blueprint for future RCTs.[70]

Targeting the RV with treatments such as levosimendan are of potential utility in PH-HFpEF patients with RV dysfunction by increasing unstressed blood volume and thereby limiting excessive splanchnic vasoconstriction and stressed blood volume delivery to the sick right heart in these patients.[96] Myotropes (e.g., myosin activators) that do not increase myocardial oxygen demand are now available and may be of use in augmenting RV contractility. A fundamental question concerns why some patients with PH-HFpEF develop RV dysfunction and others do not. Molecular markers of RV compensation or that predict decompensation may identify patients more likely to respond to myotropes.

Device-based therapeutics in PH-HFpEF

Finally, novel device-based therapeutics may have a role in PH-HFpEF (Table 5). Splanchnic denervation to improve venous capacitance in patients with PH-HFpEF who frequently develop cardiorenal syndrome with high central venous pressures is currently in development.[97, 98] Subgroup analysis of the results of the ongoing REBALANCE-HF trial could provide insight into patients with PH-HFpEF and Cpc-PH. Improving splanchnic venous capacitance increases unstressed blood volume and decreases stress blood volume. Increased stressed blood volume is an important pathophysiologic factor in HFpEF, particularly in obesity-related HFpEF, as it has been shown to impact RV-PA coupling and may provide insight into the progression from HFpEF to PH-HFpEF.[99] Another device with potential applicability to PH-HFpEF involves percutaneous mechanical unloading of the PA with a gas-filled balloon that inflates and deflates during each cardiac cycle thereby restoring central PA compliance.[100] This device, which is under development in PAH, may also be a novel therapeutic in PH-HFpEF patients in whom proximal PA stiffening is a major problem and more common than distal PA stiffening. Finally, pulmonary artery denervation improves PVR and increases 6MWD in patients with PAH and may also be effective in patients with PH-HFpEF.

Conclusion

PH-HFpEF is a growing epidemic with high morbidity, mortality, and no treatment. The clear unmet need and lethal nature of PH-HFpEF must be met with novel solutions at all

levels of therapeutic development. We highlight the critical knowledge gaps in PH-HFpEF and offer scientific directions for closing these gaps (Table 1), with a hope to develop novel treatments for patients with PH-HFpEF in the near future.

References

Uncategorized References

1. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, Barber D, Johnson A, Doliszny KM and Archer SL. Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension: A Population-Based Cohort Study in Ontario, Canada. Circ Cardiovasc Qual Outcomes 2018;11:e003973. [PubMed: 29444925]
2. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT and Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26. [PubMed: 19324256]
3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG and Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53.
4. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M and Group ESCSD. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. [PubMed: 26320113]
5. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, American College of Cardiology Foundation Task Force on Expert Consensus D, American Heart A, American College of Chest P, American Thoracic Society I and Pulmonary Hypertension A. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–619. [PubMed: 19389575]
6. Robbins IM, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, Fong PP and Newman JH. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. Circ Heart Fail 2014;7:116–22. [PubMed: 24297689]
7. Fox BD, Shimony A, Langleben D, Hirsch A, Rudski L, Schlesinger R, Eisenberg MJ, Joyal D, Hudson M, Boutet K, Serban A, Masetto A and Baron M. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. Eur Respir J 2013;42:1083–91. [PubMed: 23258775]
8. D'Alto M, Romeo E, Argiento P, Motoji Y, Correra A, Di Marco GM, Iacono AM, Barracano R, D'Andrea A, Rea G, Sarubbi B, Russo MG and Naeije R. Clinical Relevance of Fluid Challenge in Patients Evaluated for Pulmonary Hypertension. Chest 2017;151:119–126. [PubMed: 27575357]
9. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G and Levine BD. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation 2013;127:55–62. [PubMed: 23172838]
10. Andersen MJ, Olson TP, Melenovsky V, Kane GC and Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. Circ Heart Fail 2015;8:41–8. [PubMed: 25342738]
11. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R and Lewis GD. Pulmonary Capillary Wedge Pressure

Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail 2018;11:e004750. [PubMed: 29695381]

12. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Farrell R, Sbarbaro JA, Schoenike MW, Houstis NE, Baggish AL, Shah RV, Nayor M, Malhotra R and Lewis GD. Exercise Pulmonary Hypertension Predicts Clinical Outcomes in Patients With Dyspnea on Effort. J Am Coll Cardiol 2020;75:17–26. [PubMed: 31918830]
13. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jais X, Parent F, Gunther S, Humbert M, Simonneau G and Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015;46:728–37. [PubMed: 26022955]
14. Borlaug BA, Nishimura RA, Sorajja P, Lam CS and Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95. [PubMed: 20543134]
15. Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, Scelsi L, D'Alto M, Olsson KM, Ulrich S, Scholtz W, Schulz U, Grunig E, Vizza CD, Staehler G, Bruch L, Huscher D, Pittrow D and Rosenkranz S. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. J Am Coll Cardiol 2016;68:368–78. [PubMed: 27443433]
16. Vanderpool RR, Saul M, Nouraie M, Gladwin MT and Simon MA. Association Between Hemodynamic Markers of Pulmonary Hypertension and Outcomes in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol 2018;3:298–306. [PubMed: 29541759]
17. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR and Brittain EL. Prognostic Effect and Longitudinal Hemodynamic Assessment of Borderline Pulmonary Hypertension. JAMA Cardiol 2017.
18. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T and Lang IM. Pulmonary Hypertension in Heart Failure. Epidemiology, Right Ventricular Function, and Survival. Am J Respir Crit Care Med 2015;192:1234–46. [PubMed: 26181215]
19. Leung CC, Moondra V, Catherwood E and Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. Am J Cardiol 2010;106:284–6. [PubMed: 20599017]
20. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD and Investigators T. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. Circ Heart Fail 2014;7:104–15. [PubMed: 24249049]
21. Melenovsky V, Hwang SJ, Lin G, Redfield MM and Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62. [PubMed: 24875795]
22. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, Roger VL and Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation 2014;130:2310–20. [PubMed: 25391518]
23. Vachiery JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I and De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53.
24. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G and Vachiery JL. Current Limitations of Invasive Exercise Hemodynamics for the Diagnosis of Heart Failure With Preserved Ejection Fraction. Circ Heart Fail 2021;14:e007555. [PubMed: 33951935]
25. Valle F WS, Mak S. The Utility of Fluid Challenge or Exercise DUring RHC in the Evaluation of PAH 2018;2021.
26. Berry NC, Manyoo A, Oldham WM, Stephens TE, Goldstein RH, Waxman AB, Tracy JA, Leary PJ, Leopold JA, Kinlay S, Opotowsky AR, Systrom DM and Maron BA. Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. Pulm Circ 2015;5:610–8. [PubMed: 26697168]
27. Huston JH, Maron BA, French J, Huang S, Thayer T, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR and Brittain EL. Association of Mild Echocardiographic Pulmonary Hypertension With Mortality and Right Ventricular Function. JAMA Cardiol 2019.

28. Obokata M, Kane GC, Sorimachi H, Reddy YNV, Olson TP, Egbe AC, Melenovsky V and Borlaug BA. Noninvasive evaluation of pulmonary artery pressure during exercise: the importance of right atrial hypertension. Eur Respir J 2020;55.
29. Shiota T. 3D echocardiography: evaluation of the right ventricle. Curr Opin Cardiol 2009;24:410–4. [PubMed: 19550311]
30. van der Zwaan HB, Geleijnse ML, McGhie JS, Boersma E, Helbing WA, Meijboom FJ and Roos-Hesselink JW. Right ventricular quantification in clinical practice: two-dimensional vs. three-dimensional echocardiography compared with cardiac magnetic resonance imaging. Eur J Echocardiogr 2011;12:656–64. [PubMed: 21810828]
31. Grunig E and Peacock AJ. Imaging the heart in pulmonary hypertension: an update. Eur Respir Rev 2015;24:653–64. [PubMed: 26621979]
32. Dong Y, Pan Z, Wang D, Lv J, Fang J, Xu R, Ding J, Cui X, Xie X, Wang X, Chen Md Y and Guo X. Prognostic Value of Cardiac Magnetic Resonance-Derived Right Ventricular Remodeling Parameters in Pulmonary Hypertension: A Systematic Review and Meta-Analysis. Circ Cardiovasc Imaging 2020;13:e010568. [PubMed: 32673506]
33. Huis In 't Veld AE, Van Vliet AG, Spruijt OA, Handoko ML, Marcus JT, Vonk Noordegraaf A and Bogaard HJ. CTA-derived left to right atrial size ratio distinguishes between pulmonary hypertension due to heart failure and idiopathic pulmonary arterial hypertension. Int J Cardiol 2016;223:723–728. [PubMed: 27573596]
34. Johns CS, Wild JM, Rajaram S, Tubman E, Capener D, Elliot C, Condliffe R, Charalampopoulos A, Kiely DG and Swift AJ. Identifying At-Risk Patients with Combined Pre- and Postcapillary Pulmonary Hypertension Using Interventricular Septal Angle at Cardiac MRI. Radiology 2018;289:61–68. [PubMed: 29969067]
35. Crawley SF, Johnson MK, Dargie HJ and Peacock AJ. LA volume by CMR distinguishes idiopathic from pulmonary hypertension due to HFpEF. JACC Cardiovasc Imaging 2013;6:1120–1121. [PubMed: 24135327]
36. Thenappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P and Rich S. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2011;4:257–65. [PubMed: 21411741]
37. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH and Brittain EL. Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension. J Am Coll Cardiol 2016;68:2525–2536. [PubMed: 27931609]
38. Thayer TE, Levinson RT, Huang S, Assad T, Farber-Eger E, Wells QS, Mosley JD and Brittain EL. BMI Is Causally Associated With Pulmonary Artery Pressure But Not Hemodynamic Evidence of Pulmonary Vascular Remodeling. Chest 2021;159:302–310. [PubMed: 32712226]
39. Ussavarungsi K, Thomas CS and Burger CD. Prevalence of metabolic syndrome in patients with pulmonary hypertension. Clin Respir J 2017;11:721–726. [PubMed: 26493968]
40. Robbins IM, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX and Byrne DW. Association of the metabolic syndrome with pulmonary venous hypertension. Chest 2009;136:31–36. [PubMed: 19188551]
41. Kholdani C, Fares WH and Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ 2015;5:220–7. [PubMed: 26064448]
42. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I and Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J 2006;27:1106–13. [PubMed: 16497687]
43. Sajkov D, Wang T, Saunders NA, Bune AJ and McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:152–8. [PubMed: 11790646]
44. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V and Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation 2017;136:6–19. [PubMed: 28381470]

45. Upshaw JN, Finkelman B, Hubbard RA, Smith AM, Narayan HK, Arndt L, Domchek S, DeMichele A, Fox K, Shah P, Clark A, Bradbury A, Matro J, Adusumalli S, Carver JR and Ky B. Comprehensive Assessment of Changes in Left Ventricular Diastolic Function With Contemporary Breast Cancer Therapy. JACC Cardiovasc Imaging 2020;13:198–210. [PubMed: 31542526]

46. Cornell RF, Ky B, Weiss BM, Dahm CN, Gupta DK, Du L, Carver JR, Cohen AD, Engelhardt BG, Garfall AL, Goodman SA, Harrell SL, Kassim AA, Jadhav T, Jagasia M, Moslehi J, O'Quinn R, Savona MR, Slosky D, Smith A, Stadtmauer EA, Vogl DT, Waxman A and Lenihan D. Prospective Study of Cardiac Events During Proteasome Inhibitor Therapy for Relapsed Multiple Myeloma. J Clin Oncol 2019;37:1946–1955. [PubMed: 31188726]

47. Montani D, Bergot E, Gunther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P, Girerd B, Natali D, Guignabert C, Perros F, O'Callaghan DS, Jais X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G and Humbert M. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128–37. [PubMed: 22451584]

48. Miller WL, Grill DE and Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail 2013;1:290–299. [PubMed: 24621932]

49. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N and Aronson D. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. Eur J Heart Fail 2015;17:74–80. [PubMed: 25388783]

50. Inampudi C, Silverman D, Simon MA, Leary PJ, Sharma K, Houston BA, Vachiery JL, Haddad F and Tedford RJ. Pulmonary Hypertension in the Context of Heart Failure With Preserved Ejection Fraction. Chest 2021.

51. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM and Redfield MM. Global Pulmonary Vascular Remodeling in Pulmonary Hypertension Associated With Heart Failure and Preserved or Reduced Ejection Fraction. Circulation 2018;137:1796–1810. [PubMed: 29246894]

52. Rossitto G, Mary S, McAllister C, Neves KB, Haddow L, Rocchiccioli JP, Lang NN, Murphy CL, Touyz RM, Petrie MC and Delles C. Reduced Lymphatic Reserve in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol 2020;76:2817–2829. [PubMed: 33303070]

53. Gorter TM, Obokata M, Reddy YNV, Melenovsky V and Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J 2018;39:2825–2835. [PubMed: 29947750]

54. Obokata M, Reddy YNV, Melenovsky V, Pislaru S and Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J 2019;40:689–697. [PubMed: 30544228]

55. Reddy YNV, Obokata M, Verbrugge FH, Lin G and Borlaug BA. Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. J Am Coll Cardiol 2020;76:1051–1064. [PubMed: 32854840]

56. Ventetuolo CE, Aliotta JM, Braza J, Chichger H, Dooner M, McGuirl D, Mullin CJ, Newton J, Pereira M, Princiotto A, Quesenberry PJ, Walsh T, Whittenhall M, Klinger JR and Harrington EO. Culture of pulmonary artery endothelial cells from pulmonary artery catheter balloon tips: considerations for use in pulmonary vascular disease. Eur Respir J 2020;55.

57. Paik DT, Tian L, Lee J, Sayed N, Chen IY, Rhee S, Rhee JW, Kim Y, Wirka RC, Buikema JW, Wu SM, Red-Horse K, Quertermous T and Wu JC. Large-Scale Single-Cell RNA-Seq Reveals Molecular Signatures of Heterogeneous Populations of Human Induced Pluripotent Stem Cell-Derived Endothelial Cells. Circ Res. 2018;123:443–450. [PubMed: 29986945]

58. Meoli DF, Su YR, Brittain EL, Robbins IM, Hemnes AR and Monahan K. The transpulmonary ratio of endothelin 1 is elevated in patients with preserved left ventricular ejection fraction and combined pre- and post-capillary pulmonary hypertension. Pulm Circ 2018;8:2045893217745019. [PubMed: 29251543]

59. Hemnes AR, Beck GJ, Newman JH, Abidov A, Aldred MA, Barnard J, Berman Rosenzweig E, Borlaug BA, Chung WK, Comhair SAA, Erzurum SC, Frantz RP, Gray MP, Grunig G, Hassoun PM, Hill NS, Horn EM, Hu B, Lempel JK, Maron BA, Mathai SC, Olman MA, Rischard FP, Systrom DM, Tang WHW, Waxman AB, Xiao L, Yuan JX, Leopold JA and Group PS.

PVDOMICS: A Multi-Center Study to Improve Understanding of Pulmonary Vascular Disease Through Phenomics. Circ Res 2017;121:1136–1139. [PubMed: 29074534]

60. Chouvarine P, Giera M, Kastenmuller G, Artati A, Adamski J, Bertram H and Hansmann G. Trans-right ventricle and transpulmonary metabolite gradients in human pulmonary arterial hypertension. Heart 2020;106:1332–1341. [PubMed: 32079620]
61. Wallner M, Eaton DM, Berretta RM, Borghetti G, Wu J, Baker ST, Feldsott EA, Sharp TE 3rd, Mohsin S, Oyama MA, von Lewinski D, Post H, Wolfson MR and Houser SR. A Feline HFpEF Model with Pulmonary Hypertension and Compromised Pulmonary Function. Sci Rep 2017;7:16587. [PubMed: 29185443]
62. Lai YC, Wang L and Gladwin MT. Insights into the pulmonary vascular complications of heart failure with preserved ejection fraction. J Physiol 2019;597:1143–1156. [PubMed: 30549058]
63. Agrawal V, Fortune N, Yu S, Fuentes J, Shi F, Nichols D, Gleaves L, Poovey E, Wang TJ, Brittain EL, Collins S, West JD and Hemnes AR. Natriuretic peptide receptor C contributes to disproportionate right ventricular hypertrophy in a rodent model of obesity-induced heart failure with preserved ejection fraction with pulmonary hypertension. Pulm Circ 2019;9:2045894019878599.
64. Meng Q, Lai YC, Kelly NJ, Bueno M, Baust JJ, Bachman TN, Goncharov D, Vanderpool RR, Radder JE, Hu J, Goncharova E, Morris AM, Mora AL, Shapiro SD and Gladwin MT. Development of a Mouse Model of Metabolic Syndrome, Pulmonary Hypertension, and Heart Failure with Preserved Ejection Fraction. Am J Respir Cell Mol Biol 2017;56:497–505. [PubMed: 28118022]
65. Ranchoux B, Nadeau V, Bourgeois A, Provencher S, Tremblay E, Omura J, Cote N, Abu-Alhayja'a R, Dumais V, Nachbar RT, Tastet L, Dahou A, Breuils-Bonnet S, Marette A, Pibarot P, Dupuis J, Paulin R, Boucherat O, Archer SL, Bonnet S and Potus F. Metabolic Syndrome Exacerbates Pulmonary Hypertension due to Left Heart Disease. Circ Res 2019;125:449–466. [PubMed: 31154939]
66. Lai YC, Tabima DM, Dube JJ, Hughan KS, Vanderpool RR, Goncharov DA, St Croix CM, Garcia-Ocana A, Goncharova EA, Tofovic SP, Mora AL and Gladwin MT. SIRT3-AMP-Activated Protein Kinase Activation by Nitrite and Metformin Improves Hyperglycemia and Normalizes Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction. Circulation 2016;133:717–31. [PubMed: 26813102]
67. Satoh T, Wang L, Espinosa-Diez C, Wang B, Hahn SA, Noda K, Rochon ER, Dent MR, Levine A, Baust JJ, Wyman S, Wu YL, Triantafyllou GA, Tang Y, Reynolds M, Shiva S, St Hilaire C, Gomez D, Goncharov DA, Goncharova EA, Chan SY, Straub AC, Lai YC, McTiernan CF and Gladwin MT. Metabolic Syndrome Mediates ROS-miR-193b-NFYA-Dependent Down Regulation of sGC and Contributes to Exercise-Induced Pulmonary Hypertension in HFpEF. Circulation 2021.
68. Aguero J, Ishikawa K, Hadri L, Santos-Gallego C, Fish K, Hammoudi N, Chaanine A, Torquato S, Naim C, Ibanez B, Pereda D, Garcia-Alvarez A, Fuster V, Sengupta PP, Leopold JA and Hajjar RJ. Characterization of right ventricular remodeling and failure in a chronic pulmonary hypertension model. Am J Physiol Heart Circ Physiol 2014;307:H1204–15. [PubMed: 25158063]
69. Reddy YNV, Obokata M, Koepp KE, Egbe AC, Wiley B and Borlaug BA. The beta-Adrenergic Agonist Albuterol Improves Pulmonary Vascular Reserve in Heart Failure With Preserved Ejection Fraction. Circ Res 2019;124:306–314. [PubMed: 30582447]
70. Burkhoff D, Borlaug BA, Shah SJ, Zolty R, Tedford RJ, Thenappan T, Zamanian RT, Mazurek JA, Rich JD, Simon MA, Chung ES, Raza F, Majure DT, Lewis GD, Preston IR and Rich S. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial. JACC Heart Fail 2021;9:360–370. [PubMed: 33839076]
71. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Pina IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M and Investigators EM-PT. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021;385:1451–1461. [PubMed: 34449189]

72. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, Wilderang U, Ohrn F, Claggett B, Langkilde AM, Petersson M and McMurray JJV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail 2021;23:1217–1225. [PubMed: 34051124]
73. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S and McKinlay SM. Spironolactone for Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine 2014;370:1383–1392. [PubMed: 24716680]
74. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, Investigators P-H and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019;381:1609–1620. [PubMed: 31475794]
75. Berry N, Mauri L, Feldman T, Komtebedde J, van Veldhuisen DJ, Solomon SD, Massaro JM and Shah SJ. Transcatheter InterAtrial Shunt Device for the treatment of heart failure: Rationale and design of the pivotal randomized trial to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure II (REDUCE LAP-HF II). Am Heart J 2020;226:222–231. [PubMed: 32629295]
76. Shah SJ. Matchmaking for the optimization of clinical trials of heart failure with preserved ejection fraction: no laughing matter. J Am Coll Cardiol 2013;62:1339–42. [PubMed: 23916923]
77. Siontis KC, Noseworthy PA, Attia ZI and Friedman PA. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. Nat Rev Cardiol 2021.
78. Huda A, Castano A, Niyogi A, Schumacher J, Stewart M, Bruno M, Hu M, Ahmad FS, Deo RC and Shah SJ. A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy. Nat Commun 2021;12:2725. [PubMed: 33976166]
79. Goto S, Mahara K, Beussink-Nelson L, Ikura H, Katsumata Y, Endo J, Gaggin HK, Shah SJ, Itabashi Y, MacRae CA and Deo RC. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. Nat Commun 2021;12:2726. [PubMed: 33976142]
80. Tison GH, Zhang J, Delling FN and Deo RC. Automated and Interpretable Patient ECG Profiles for Disease Detection, Tracking, and Discovery. Circ Cardiovasc Qual Outcomes 2019;12:e005289. [PubMed: 31525078]
81. Shah SJ. Innovative Clinical Trial Designs for Precision Medicine in Heart Failure with Preserved Ejection Fraction. J Cardiovasc Transl Res 2017;10:322–336. [PubMed: 28681133]
82. Andersen MJ, Hwang SJ, Kane GC, Melenovsky V, Olson TP, Fetterly K and Borlaug BA. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: pulmonary artery coupling in heart failure with preserved ejection fraction. Circ Heart Fail 2015;8:542–50. [PubMed: 25857307]
83. Tampakakis E, Shah SJ, Borlaug BA, Leary PJ, Patel HH, Miller WL, Kelemen BW, Houston BA, Kolb TM, Damico R, Mathai SC, Kasper EK, Hassoun PM, Kass DA and Tedford RJ. Pulmonary Effective Arterial Elastance as a Measure of Right Ventricular Afterload and Its Prognostic Value in Pulmonary Hypertension Due to Left Heart Disease. Circ Heart Fail 2018;11:e004436. [PubMed: 29643065]
84. Assad TR, Brittain EL, Wells QS, Farber-Eger EH, Halliday SJ, Doss LN, Xu M, Wang L, Harrell FE, Yu C, Robbins IM, Newman JH and Hemnes AR. Hemodynamic evidence of vascular remodeling in combined post- and precapillary pulmonary hypertension. Pulm Circ 2016;6:313–21. [PubMed: 27683608]
85. McGoon MD, Ferrari P, Armstrong I, Denis M, Howard LS, Lowe G, Mehta S, Murakami N and Wong BA. The importance of patient perspectives in pulmonary hypertension. Eur Respir J 2019;53.

86. Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R and Fischler M. Measurement of quality of life in pulmonary hypertension and its significance. Eur Respir J 2006;28:808–15. [PubMed: 16707511]

87. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J and Nicklas BJ. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA 2016;315:36–46. [PubMed: 26746456]

88. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP and Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659–67. [PubMed: 20852060]

89. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine B, Drazner M and Berry J. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33–40. [PubMed: 25399909]

90. Pandey A, Garg S, Khunger M, Garg S, Kumbhani DJ, Chin KM and Berry JD. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. Circ Heart Fail 2015;8:1032–43. [PubMed: 26185169]

91. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M and Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780–91. [PubMed: 21996391]

92. Hemnes AR, Silverman-Loyd L, Huang S, MacKinnon G, Annis J, Whitmore CS, Mallugari R, Oggs RN, Hekmat R, Shan R, Huynh PP, Yu C, Martin SS, Blaha MJ and Brittain EL. A Mobile Health Intervention to Increase Physical Activity in Pulmonary Arterial Hypertension. Chest 2021.

93. ClinicalTrials.gov. NCT03153111: A Study to Evaluate Whether Macitentan is an Effective and Safe Treatment for Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease (SERENADE). 2021.

94. ClinicalTrials.gov. NCT03037580: Oral Treprostinil in Subjects With Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction. 2021.

95. ClinicalTrials.gov. NCT03541603: Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF (HELP). 2021.

96. Brener MI, Hamid NB, Sunagawa K, Borlaug BA, Shah SJ, Rich S and Burkhoff D. Changes in Stressed Blood Volume with Levosimendan in Pulmonary Hypertension from Heart Failure with Preserved Ejection Fraction: Insights Regarding Mechanism of Action From the HELP Trial. J Card Fail 2021.

97. Fudim M, Ponikowski PP, Burkhoff D, Dunlap ME, Sobotka PA, Molinger J, Patel MR, Felker GM, Hernandez AF, Litwin SE, Borlaug BA, Bapna A, Sievert H, Reddy VY, Engelman ZJ and Shah SJ. Splanchnic nerve modulation in heart failure: mechanistic overview, initial clinical experience, and safety considerations. Eur J Heart Fail 2021;23:1076–1084. [PubMed: 33886137]

98. ClinicalTrials.gov. NCT04592445: Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF (Rebalance-HF). 2021;2021.

99. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, Takahashi N, Sunagawa K and Borlaug BA. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:1648–1658. [PubMed: 34053158]

100. Gerges C, Vollmers K, Pritzker MR, Gainor J, Scandurra J, Weir EK and Lang IM. Pulmonary Artery Endovascular Device Compensates for Loss of Vascular Compliance in Pulmonary Arterial Hypertension. J Am Coll Cardiol 2020;76:2284–2286. [PubMed: 33153589]

Table 1:

Current Problems in PH-HFpEF and Potential Solutions

PH-HFpEF Definition, Prevalence, and Incidence	
Problem	**Approach**
Bias among retrospective cohorts with missing data and potentially poorly generalizable populations	Prospective, multicenter studies with shared phenotyping protocols to understand PH prevalence and progression among patients with HFpEF (e.g., NIH Heart Share network)
The prevalence and incidence of PH-HFpEF are unknown due to lack of longitudinal data with standardized phenotyping	Data from well-phenotyped, longitudinal EHR cohorts (despite limitations of such data) can provide prevalence and incidence rates specific to patients seeking care
Diagnosis and Interpretation of Hemodynamic Data	
Problem	**Approach**
Lack of standardization of provocative maneuver protocols and inconsistent interpretation of results	Standardize protocols and perform validation studies using provocative maneuvers
Need for reliable non-invasive evaluation of PH severity and etiology in HFpEF	Prospective, rigorous, non-invasive studies linked to invasive data to validate echo/exercise predictors of Ipc-PH and Cpc-PH
Unclear role of invasive exercise testing to guide therapy and monitor for progression of PH-HFpEF	Prospective outcomes studies to assess the importance of invasive exercise testing to guide therapy as well as monitor for progression of PH-HFpEF
Non-Cardiac Contributors to PH Risk in HFpEF	
Problem	**Approach**
Need to understand demographic and clinical risk factors for PH in HFpEF – are observed demographic discrepancies based on biologic differences or related to differences in treatment/socioeconomic/environmental factors?	Studies focusing on the role of sex and socioeconomic/environmental exposures as biologic variables
High prevalence of non-cardiac comorbidities may contribute or even drive PH in some patients with HFpEF	•Studies with more detailed non-cardiac phenotyping (particularly disordered breathing and parenchymal lung disease) to understand drivers of overlapping PH etiologies. •Studies focused on understanding the impact of the obesity epidemic on PH-HFpEF risk and interventions (e.g., metformin, mobile health, bariatric surgery) that may reduce or mitigate PH risk in obesity.
Combined Pre-and Post-Capillary PH: Diagnosis and Pathophysiology	
Problem	**Approach**
The prevalence, incidence, and clinical risk factors for Cpc-PH are unclear	Prospective studies with standardized clinical and molecular phenotyping can shed more light on the epidemiology of Cpc-PH
Lack of robust non-invasive markers to identify Cpc-PH	Future research should focus on determining non-invasive imaging or biomarker surrogates for PH-HFpEF and subphenotypes.
Pathophysiology of PH and Translational Approaches to Understand Vascular Remodeling in HFpEF	
Problem	**•Approach**
Poor understanding of Cpc-PH pathophysiology due to lack of molecular data and relevant biospecimens	•Leverage existing data from PVDOMICS and future results of the HeartShare program. •Investment in innovative approaches to study vascular biology including harvesting PA endothelial cells, peripheral and transpulmonary blood samples, inducible stem cells, and efforts to collect lung samples from patients for molecular studies.
Animal Models of PH-HFpEF	
Problem	**Approach**
Lack of a single model that fits all aspects of the disease due to phenotypic heterogeneity and multifactorial nature of the disease.	Selection of appropriate fit-for-purpose models and comprehensive characterization of multidimensional phenotypical readouts.
Lack of large animal models close to human translation	Development of large animal models of PH-HFpEF that can expedite human translation

PH-HFpEF Definition, Prevalence, and Incidence	
Problem	**Approach**
Treatment Approaches	
Problem	**Approach**
Heterogeneity in the diagnostic method and definition of PH in clinical trials	Developing a universal definition of PH-HFpEF for inclusion in clinical trials
Enrollment of heterogeneous patients with HFpEF in RCT's and Challenges identifying eligible patients for trials	Precision medicine trials that target specific therapies to specific HFpEF subphenotypes, such as PH-HFpEFNovel RCT designs such as umbrella trials, bucket trials, and adaptive trialsIdentify non-invasive imaging or biomarker surrogates for PH-HFpEF and subphenotypes Create surrogate-based *a priori* sub-group analyses to enhance RCT interpretation.•Leverage EHR data and machine learning to identify eligible trial participants

Table 2.

Current Hemodynamic Definitions of Pulmonary Hypertension and PH-HFpEF

Hemodynamic Definition of Pulmonary Hypertension [3]		
Definitions	**Hemodynamic Criteria**	**WHO Groups**
Pre-capillary PH	mPAP >20mmHg PAWP ≤ 15mmHg PVR ≥3 WU	1,3,4,5
Isolated post-capillary PH	mPAP >20mmHg PAWP > 15mmHg PVR <3 WU	2,5
Combined pre- and post-capillary PH	mPAP >20mmHg PAWP > 15mmHg PVR ≥3 WU	2,5
Components of PH-HFpEF Definition in Clinical Trials and Epidemiologic studies		
Modality	**Methods or Criteria Used**	
Clinical	Elevated BNP or NT-pro-BNP Heart Failure Signs and Symptoms (Framingham Criteria) Heart Failure Hospitalization	
Echocardiography	LVEF ≥ 40–55% and RVSP > 35–40mmHg or TRV > 2.9 m/s	
Hemodynamic	mPAP≥ 25mmHg TPG ≥ 12mmHg PAWP ≥ 15–20mmHg or LVEDP >15 **Confrontational Fluid Challenge** 500mL of Normal Saline over 5–10minutes; PAWP>15mmHg [6, 7] Normal Saline at 7mL/kg over 5–10minutes; PAWP≥18mmHg[8] Normal Saline at 100–200mL/min over two 7minute intervals; PAWP/saline slope ≥25 (±12) mmHg*L*min[9] Normal Saline 10mL/kg; ≥21(±4)mmHg[10] **Exercise** Upright cycle ergometer with continuous incremental ramp cycle (5–30W/min) at 60rpm; mPAP/CO >2–3mmHg/L/min [11, 12] Supine cycle ergometry at 60rpm increasing workload 10–30W every 3–5minutes; mPAP>30mmHg[13] Weighted (4lb) Arm Adduction or Supine cycle ergometry 20W workload x 5 minutes then increasing 10W every 3 minutes; PAWP ≥ 25mmHg [10, 14]	

WHO: World Health Organizations; PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; LVEF: left ventricular ejection fraction; RVSP: right ventricular systolic pressure; TRV: tricuspid regurgitant velocity; TPG: transpulmonary gradient; W:Watts

Table 3.
Prevalence of Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction

There is significant variability in the definition of PH-HFpEF, modality of evaluation and prevalence, however, PH is present in a substantial proportion of the population, ranging from 36–83%.

Study	Years	Population	Diagnostics	Definition	Prevalence of PH	Severity
Lam et al [2]	2003–2005	Olmsted County Heart Failure Surveillance Study	Echo estimated PASP	•Framingham criteria •LVEF ≥50% •Echo PASP >35 mm Hg	83%	PASP= 48 (37–56) mm Hg
Gerges et al [18]	Retrospective Cohort 1996–2003	Medical University of Vienna	•Echo, RHC	•Heart Failure signs and symptoms •LVEF≥45% •mPAP≥25 mm Hg	54.4%	Cpc-PH mPAP 45.6±12.8 mm Hg Ipc-PH mPAP 36.4± 8.1 mm Hg
	Prospective Cohort 2012–2013				63%	Cpc-PH mPAP 44.2±13.2 mm Hg Ipc-PH mPAP 34.3±7.0 mm Hg
Leung et al [19]	1996–2007	Dartmouth Dynamic Registry	LHC/RHC	•LVEDP >15 •LVEF ≥50% •mPAP >25	52.5%	mPAP 34.2±7.8 mm Hg
Shah et al[20]	2006–2012	TOPCAT-echocardiography cohort	Echo measure TRV	•LVEF ≥45% •HF hospitalization or elevated BNP/NT-proBNP •TRV >2.9m/s	36%	Mean TRV 3.28 (±0.33) m/s
Melenovsky et al [21]	2005–2012	Mayo Clinic	Echo, RHC	•Framingham criteria •LVEF ≥50% •PAWP≥15mmHg •mPAP > 25 mm Hg	81%	mPAP 36±11 mm Hg
Mohammed et al [22]	2003–2009	Mayo Clinic, Olmstead County HFpEF Cohort	Echo	•Framingham criteria •LVEF ≥50% •PASP>40mmHg	64.5%	
Ho et al[12]	2006–2017	Massachusetts General Hospital	Invasive CPET	•EF ≥50% •mPAP/CO >3mmHg/L/min	41% (exercise PH)	

PASP: pulmonary artery systolic pressure; RHC: right heart catheterization; Cpc-PH: combined pre- and post-capillary PH; Ipc-PH: isolated post-capillary PH; LVEDP: left ventricular end diastolic pressure; LVEF: left ventricular ejection fraction; HF: heart failure; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; TRV: tricuspid regurgitant velocity; PAWP: pulmonary artery wedge pressure; CPET: cardiopulmonary exercise test mPAP: mean pulmonary arterial pressure; CO; cardiac output

Table 4:

Animal Models of PH-HFpEF

	Experimental PH-HFpEF models/ Comorbidities and disease modifiers	Type of animal species	Advantages	Limitations
Single-hit models	Aortic banding	Mouse Rat Cat Pig	•Reliable and commonly used model for examining cardiac factors without interference from additional comorbidities •Disease phenotypes have been extensively characterized	•The acute increase in afterload does not reflect the pathophysiology of human HFpEF •Prolonged banding (after ~4weeks) leads to LV dilation and systolic heart failure (HFrEF)
	Leptin-deficient ob/ob mouse	Mouse	•No surgery or additional treatment is needed	•Incomplete characterization of PH-HFpEF in this model
	High-fat diet (HFD)	Mouse	•Can be combined with specific genetic manipulations	•Not all mouse strains develop HFD-induced PH-HFpEF •Mild PH-HFpEF phenotypes in susceptible mouse strains
Multi-hit models	Supra-coronary banding + HFD + olanzapine	Rat	•Recapitulate many features of human disease •Permits omics analyses of specific vessel types	•Exercise intolerance, kidney dysfunction and skeletal muscle abnormalities have not been reported
	SU5416 + obese ZSF1 rat	Rat	•Recapitulate many of the key features of human disease, including comorbidities, systemic alterations, physical inactivity, and exercise intolerance •Reproducible •Develop exercise-induced PH-HFpEF during treadmill training	•Relatively expensive •Female obese ZSF1 rats are resistant to the development of hyperglycemia and proteinuria
Large-Animal Model	Banding of pulmonary veins	Pig	•Recapitulates global vascular remodeling observed in humans	•Requires advanced surgical expertise •May not model the effect of comorbidities on pulmonary hypertension (e.g., systemic hypertension)

Table 5:

Selected Recent Clinical Trials Applicable to PH-HFpEF

Acronym/ Trial Number	Intervention	Design	Phase	Target HFpEF population	Primary Endpoint	Comments
Vasodilation						
SERENADE NCT03153111	Macitentan 24–52 weeks	Multicenter Double-blind Randomized Placebo-controlled	2b	HFpEF (EF ≥ 40%) pulmonary vascular disease RV dysfunction	Change in NT-pro-BNP	Enrichment design Terminated early due to slow enrollment; open label extension; results pending
SOUTHPAW NCT03037580	Oral Treprostinil, 24 weeks	Multicenter Double-blind Randomized Placebo-controlled	3	HFpEF (EF ≥ 45%) RHC confirmed WHO Group 2 PH	Change in 6-minute walk distance	Enrichment design, Terminated early due to slow enrollment; open label extension
HELP-PH-HFpEF[70]	Intravenous Levosimendan, 6 weeks	Multicenter Double-blind Randomized Placebo-controlled	2	WHO Group 2 PH HFpEF (EF ≥ 40%) PAP ≥ 35 mm Hg PCWP ≥ 20 mm Hg	Change in PCWP with bicycle exercise	Enrichment design; Randomization: ≥ 4 mmHg ↓ PCWP from baseline exercise w/ ≤ 10% ↓ CI. Levosimendan did not reduce exercise-PCWP but did reduce PCWP incorporating data from rest and exercise and increased 6MWD
DYNAMIC NCT02744339	Riociguat 26 weeks	Multicenter Double-blind Randomized Placebo-controlled	2	WHO Group 2 PH HFpEF (EF ≥ 50%) mPAP ≥ 25 mm Hg PCWP > 15 mm Hg	Change in CO by RHC	
BEAT HFpEF[69]	Inhaled Albuterol Acute intervention	Single center Randomized Placebo-controlled	2	HFpEF (EF ≥ 50%) PCWP >15	Change in PVR at 20-Watt exercise	Albuterol improved exercise PVR as compared with placebo (−0.6±0.5 versus +0.1±0.7 WU; P=0.003).
Nebivolol NCT02053246	Nebivolol (β3 agonist) 18 weeks	Single center study	4	HFpEF(EF ≥ 45%) mPAP ≥ 25 PCWP ≥ 15	Change in PVR	Low enrollment
Metabolic						
Metformin for PH-HFpEF NCT03629340	Metformin 12 weeks	Multicenter Randomized Placebo-controlled Crossover	2	RHC confirmed PH-HFpEF mPAP ≥ 25 mm Hg PCWP ≥ 15 mm Hg TPG ≥ 12 mm hg Metabolic syndrome	Change in mPAP with submaximal exercise	
EMPEROR-Preserved[71]	Empagliflozin, ~24 months	Multicenter Double-blind Randomized Placebo-controlled	3	HFpEF (EF ≥ 40%) Elevated NT-pro-BNP	Composite: CV death or HF hospitalization	
DELIVER[72]	Dapagliflozin Event driven trial	International, Double-blind, Randomized, Placebo-Controlled	3	HFpEF (EF≥ 40%) Structural heart disease	Composite: CV death, HF hospitalization, or urgent HF visit	

Acronym/ Trial Number	Intervention	Design	Phase	Target HFpEF population	Primary Endpoint	Comments
Vasodilation						
PRESERVED-HF NCT03030235	Dapagliflozin, 12 weeks	Multicenter Randomized Double-blind Placebo-controlled	4	HFpEF (EF≥ 45%) Elevated NT-pro-BNP or BNP	Change in heart failure related health status (KCCQ)	
Device-based						
REBALANCE-HF NCT04592445	Right greater splanchnic nerve ablation	Multicenter Double-blind Randomized Sham-control	Feasibility	HFpEF (EF ≥ 50%) PCWP ≥25 mm Hg with supine exercise	Change in mean PCWP at rest, exercise and with provocative maneuvers	
ASPIRE PH NCT04555161	Implanted device in the central PA	Multicenter Open label	Feasibility	WHO Group 1 PAH, potential for applicability to Group 2 PH	Safety: Device or procedure-related serious adverse events	Improves central PA compliance
TROPHY II NCT03611270	PA Denervation via TIVUS system	Multicenter Open Label		Cpc-PH HFpEF or HFrEF	Procedural related adverse events up to 30 days post-procedure	

Abbreviations: HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, PAH – pulmonary arterial hypertension, PA – pulmonary artery, PAWP – pulmonary artery wedge pressure, mPAP – mean pulmonary artery pressure, TPG – transpulmonary gradient, PVR - pulmonary vascular resistance, and CO _ cardiac output, PAP – pulmonary artery pressure, KCCQ – Kansas City Cardiomyopathy Questionnaire, RV- right ventricle, EF – ejection fraction, RHC – right heart catheterization, WHO – World Health Organization, BNP – Brain natriuretic peptide, NT-proBNP – N-terminal pro brain natriuretic peptide, Cpc-PH – combined post-and pre-capillary PH.