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AHA SCIENCE ADVISORY

Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: A Science Advisory From the American Heart Association

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ABSTRACT: This science advisory focuses on the need to better understand the epidemiology, pathophysiology, and treatment of pulmonary hypertension in patients with heart failure with preserved ejection fraction. This clinical phenotype is important because it is common, is strongly associated with adverse outcomes, and lacks evidence-based therapies. Our goal is to clarify key knowledge gaps in pulmonary hypertension attributable to heart failure 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 into noncardiac contributors to pulmonary hypertension risk, optimized animal models, and further molecular studies in patients with combined precapillary and postcapillary pulmonary hypertension. We highlight translational approaches that may provide important biological insight into pathophysiology and reveal new therapeutic targets. Last, 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 science advisory provides a synthesis of important knowledge gaps, culminating in a collection of specific research priorities that we argue warrant investment from the scientific community.

Key Words: AHA Scientific Statements ■ heart failure ■ hypertension, pulmonary

Heart failure (HF) 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) is among the strongest risk factors for adverse outcomes in HFpEF.[2] Despite this recognition, no evidence-based therapies exist for PH attributable 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 science advisory is to clarify key knowledge gaps in PH-HFpEF and to suggest scientific directions for addressing such gaps, which we synthesize in Table 1.

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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	Prospective, multicenter studies with shared phenotyping protocols to understand PH prevalence and progression among patients with HFpEF (eg, National Institutes of Health Heart Share network)
Unknown prevalence and incidence of PH-HFpEF attributable to a lack of longitudinal data with standardized phenotyping	Data from well-phenotyped, longitudinal electronic health record 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 noninvasive evaluation of PH severity and cause in HFpEF	Prospective, rigorous, noninvasive studies linked to invasive data to validate echocardiographic/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 and monitor for progression of PH-HFpEF
Noncardiac 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 biological differences or related to differences in treatment/socioeconomic/environmental factors?	Studies focusing on the role of sex and socioeconomic/environmental exposures as biological variables
High prevalence of noncardiac comorbidities may contribute or even drive PH in some patients with HFpEF	Studies with more detailed noncardiac phenotyping (particularly disordered breathing and parenchymal lung disease) to understand drivers of overlapping PH causes Studies focused on understanding the impact of the obesity epidemic on PH-HFpEF risk and interventions (eg, metformin, mobile health, bariatric surgery) that may reduce or mitigate PH risk in obesity
Cpc-PH: diagnosis and pathophysiology	
Problem	Approach
Unclear prevalence, incidence, and clinical risk factors for Cpc-PH	Prospective studies with standardized clinical and molecular phenotyping to shed more light on the epidemiology of Cpc-PH
Lack of robust noninvasive markers to identify Cpc-PH	Future research focused on determining noninvasive 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 attributable to lack of molecular data and relevant biospecimens	Leverage existing data from the Pulmonary Vascular Disease Phenomics Consortium and future results of the HeartShare program Invest 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 because of phenotypic heterogeneity and the 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
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 RCTs and challenges identifying eligible patients for trials	Developing precision medicine trials that target specific therapies to specific HFpEF subphenotypes such as PH-HFpEF Using novel RCT designs such as umbrella trials, bucket trials, and adaptive trials Identifying noninvasive imaging or biomarker surrogates for PH-HFpEF and subphenotypes Creating surrogate-based a priori subgroup analyses to enhance RCT interpretation Leveraging electronic health record data and machine learning to identify eligible trial participants

Cpc-PH indicates combined precapillary and postcapillary pulmonary hypertension; HFpEF, heart failure with preserved ejection fraction; Ipc-PH, isolated postcapillary pulmonary hypertension; PA, pulmonary artery; PH, pulmonary hypertension; PH-HFpEF, pulmonary hypertension attributable to heart failure with preserved ejection fraction; and RCT, randomized controlled trial.

Table 2. Current Hemodynamic Definitions of PH and PH-HFpEF

Hemodynamic definition of PH[3]		
Definitions	Hemodynamic criteria	WHO Groups
Precapillary PH	mPAP >20 mm Hg PAWP ≤15 mm Hg PVR ≥3 WU	1, 3–5
Ipc-PH	mPAP >20 mm Hg PAWP >15 mm Hg PVR <3 WU	2, 5
Cpc-PH	mPAP >20 mm Hg PAWP >15 mm Hg PVR ≥3 WU	2, 5
Components of PH-HFpEF definition in clinical trials and epidemiological studies		
Modality	Methods or criteria used	
Clinical	Elevated BNP or NT-proBNP HF signs and symptoms (Framingham criteria) HF hospitalization	
Echocardiography	LVEF ≥40%–55% and RVSP >35–40 mm Hg or TRV >2.9 m/s	
Hemodynamic	mPAP ≥25 mm Hg TPG ≥12 mm Hg PAWP ≥15–20 mm Hg or LVEDP >15 mm Hg Confrontational fluid challenge 500 mL normal saline over 5–10 min; PAWP >15 mm Hg[6,7] Normal saline at 7 mL/kg over 5–10 min; PAWP ≥18 mm Hg[8] Normal saline at 100–200 mL/min over two 7-min intervals; PAWP/saline slope ≥2.5±12 mm Hg/L/min[9] Normal saline 10 mL/kg; PAWP ≥21±4 mm Hg[10] Exercise Upright cycle ergometer with continuous incremental ramp cycle (5–30 W/min) at 60 rpm; mPAP/CO >2–3 mm Hg/L/min[11,12] Supine cycle ergometry at 60 rpm, increasing workload 10–30 W every 3–5 min; mPAP >30 mm Hg[13] Weighted (4 lb) arm adduction or supine cycle ergometry, 20-W workload for 5 min, then increasing 10 W every 3 min; PAWP ≥25 mm Hg[10,14]	

BNP indicates brain natriuretic peptide; CO, cardiac output; Cpc-PH, combined precapillary and postcapillary pulmonary hypertension; HF, heart failure; Ipc-PH, isolated postcapillary pulmonary hypertension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PH-HFpEF, pulmonary hypertension attributable to heart failure with preserved ejection fraction; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; TPG, transpulmonary gradient; TRV, tricuspid regurgitant velocity; WHO, World Health Organizations; and WU, Wood units.

PH-HFpEF DEFINITION, PREVALENCE, AND INCIDENCE

The definition of HFpEF varies widely among societal statements, guidelines, and clinical trials. Equally varied is the PH-HFpEF definition, which often is based on echocardiographic data rather than the gold standard, right-sided 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 epidemiological studies. Most data on HFpEF prevalence are derived from registries and electronic health record–based studies. Consequently, important details on PH subgroups are unavailable or potentially inaccurate because these sources rely primarily on international classification of disease codes and are associated with selection bias toward 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 with or without PH is important because individuals with mean pulmonary artery (PA) pressure ≥19 mm Hg and those with mildly elevated pulmonary pressure and pulmonary vascular resistance (PVR) ≥2.2 Wood units are at particularly elevated mortality risk.[17]

The reported prevalence of PH-HFpEF varies widely, depending on the population (clinical trial participants versus hospital-based cohorts), diagnostic approach (echocardiography or RHC), and the definition used (Table 3). For example, the prevalence of a tricuspid regurgitant velocity >2.9 m/s was 36% among TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) echocardiography substudy 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 was suboptimal for guiding information on prevalence. Longitudinal data on PH incidence and progression among well-phenotyped PH-HFpEF cohorts are also lacking.

Table 3. Prevalence of PH in HFpEF

Study	Years	Population	Diagnostics	Definition	Prevalence of PH, %	Severity
Lam et al[2]	2003–2005	Olmsted County Heart Failure Surveillance Study	Echocardiography-estimated PASP	Framingham criteria LVEF ≥50% Echocardiography PASP >35 mm Hg	83	PASP 48 (37–56) mm Hg
Gerges et al[18]	Retrospective cohort 1996–2003	Medical University of Vienna	Echocardiography, RHC	HF 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 mm Hg LVEF ≥50% mPAP >25 mm Hg	52.5	mPAP 34.2±7.8 mm Hg
Shah et al[20]	2006–2012	TOPCAT, echocardiography cohort	Echocardiography-measured TRV	LVEF ≥45% HF hospitalization or elevated BNP/NT-proBNP TRV >2.9 m/s	36	Mean TRV 3.28±0.33 m/s
Melenovsky et al[21]	2005–2012	Mayo Clinic	Echocardiography, RHC	Framingham criteria LVEF ≥50% PAWP ≥15 mm Hg mPAP > 25 mm Hg	81	mPAP 36±11 mm Hg
Mohammed et al[22]	2003–2009	Mayo Clinic, Olmstead County HFpEF cohort	Echocardiography	Framingham criteria LVEF ≥50% PASP >40 mm Hg	64.5	
Ho et al[12]	2006–2017	Massachusetts General Hospital	Invasive CPET	EF ≥50% mPAP/CO >3 mm Hg/L/min	41 (exercise PH)	

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% to 83%.

BNP indicates brain natriuretic peptide; CO, cardiac output; Cpc-PH, combined precapillary and postcapillary pulmonary hypertension; CPET, cardiopulmonary exercise test; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; Ipc-PH, isolated postcapillary pulmonary hypertension; LHC, left-sided heart catheterization; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; RHC, right-sided heart catheterization; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial; and TRV, tricuspid regurgitant velocity.

DIAGNOSIS OF PH-HFpEF AND INTERPRETATION OF HEMODYNAMIC DATA

In patients with suspected PH-HFpEF, RHC usually reveals PH, elevated PA wedge pressure (PAWP), and normal or elevated PVR. However, in some cases, PH may be present without a significant elevation of PAWP (often in the setting of diuretic therapy). Provocative maneuvers with exercise or fluid challenge can unmask left ventricular 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 and 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 varies among upright, supine, and semirecumbent by center, as do workload protocols and even PH-HFpEF hemodynamic definitions (ie, mean PA pressure/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 patients with PH have a low resting PAWP that subsequently increases with provocation, they are generally categorized as having PH-HFpEF or PH with occult left-sided heart disease. It remains unclear whether these patients are simply adequately diuresed or the resting PAWP is persistently low and they develop hemodynamic congestion primarily with exercise or other provocation. Interpretation of provocative maneuvers must incorporate pretest probability of disease, an important factor that can be difficult to standardize.

There is a critical need for a noninvasive tool to fully characterize the presence of pulmonary vascular dysfunction, right ventricle (RV)–PA coupling, and intracardiac filling pressures in HFpEF. An ideal tool would differentiate patients with HFpEF without PH from those

with isolated postcapillary PH (Ipc-PH) versus combined precapillary and postcapillary PH (Cpc-PH) noninvasively. One such measure may be noninvasive assessment of RV-PA coupling (tricuspid annular plane systolic excursion/PA systolic pressures), which is associated with increased mortality risk, even when the estimated PA systolic pressure is nearly normal.[27] Careful echocardiographic assessment of RV-PA coupling, estimated PVR, PA acceleration time, or composites of echocardiographic features may help stratify risk in patients with PH-HFpEF and drive further testing. However, echocardiography, although widely available and noninvasive, 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 PA systolic pressure at peak exercise.[28] Although 3-dimensional echocardiography may offset some of these limitations, it is not widely used in mainstream clinical practice.[29,30] Cardiac magnetic resonance imaging 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 cardiac magnetic resonance imaging (or cardiac computed tomography) can help differentiate between PH-HFpEF and PAH.[33–35] Nevertheless, appropriately diagnosing and prognosticating patients with PH requires invasive testing because at present key hemodynamic parameters, including PAWP, PVR, and cardiac output, are not valid measures with noninvasive imaging tools. Provocative maneuvers during echocardiography may influence the pretest probability of PH on RHC and provide insight into the disease, particularly under circumstances in which valvular disease or left ventricular dysfunction is observed.

NONCARDIAC CONTRIBUTORS TO PH RISK IN HFpEF

The specific effects of age, sex, race, and comorbid conditions on PH risk in patients with HFpEF require further study. Female sex and Black race were risk factors for PH in unselected cohorts referred for diagnostic testing, but it is unclear whether this is driven by treatment differences, socioeconomic status, or both.[36,37] Systematically collected data examining potential influences of other comorbidities (eg, sleep disordered breathing, atrial arrhythmias, and lung disease) on PH risk or outcomes in HFpEF are lacking. There is evidence that obesity alone increases PA pressure (but not pulmonary vascular remodeling).[38] Obesity and metabolic syndrome coexist in up to 50% of patients with PH attributable to left-sided heart disease, 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 are suspected to contribute to PH through 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 in mean PA pressure and PVR, although a direct pathophysiological 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 because the obese-HFpEF phenotype is 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 tyrosine kinase inhibitor dasatinib) may also cause direct pulmonary vascular dysfunction.[47] These observations highlight the need for clinical and epidemiological vigilance with respect to PH-HFpEF risk as new cancer therapeutics emerge and cancer-related cardiovascular surveillance becomes standard of care.

Cpc-PH: DIAGNOSIS AND PATHOPHYSIOLOGY

Cpc-PH differs from Ipc-PH by the presence of PVR ≥3 Wood units. The prevalence of Cpc-PH among retrospective HF referral populations ranges from 12% to 40%.[18,37,48,49] It is important to distinguish Cpc-PH from Ipc-PH because Cpc-PH is associated with worse outcomes, and in contrast to patients with Ipc-PH, patients with Cpc-PH are 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 because 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 are typically cited as the primary drivers 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. Various theories exist about the development of Cpc-PH in HFpEF. Although generally regarded as pathological, it is possible that pulmonary vascular changes in HFpEF may be adaptive, working specifically to protect the left side of the 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 who develop disease akin to a pulmonary veno-occlusive forme fruste rather than PAH per se. There may be subtypes of Cpc-PH that are 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 (eg, obesity, insulin resistance) may also increase the 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, although 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. The available data suggest that pulmonary vascular pathology in PH-HFpEF is multifactorial and involves complex systemic alterations. Patients with PH-HFpEF 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 patients with HFpEF display >50% venous intimal thickening, indicating that individual patients who develop the disease can vary markedly. These structural changes are observed regardless of left ventricular systolic function but appear particularly striking in HFpEF. Lymphatic function and drainage are impaired in obesity, metabolic syndrome, and chronic inflammatory states, all recognized comorbidities of HFpEF. Evidence is emerging 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 RV pathology and emerging evidence for unique RV pathophenotypes also warrant 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 on the basis of evidence that the RV may decline out of proportion to changes in left ventricular structure and function in patients with HFpEF.[54] Recent data also suggest a potential contribution of atrial myopathy attributable to atrial fibrillation in promoting pulmonary vascular disease and RV dysfunction in patients with HFpEF.[55] Whether atrial fibrillation management (ie, rhythm versus 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 patients with HF undergoing thoracic surgery or postmortem 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 the histopathology of PH-HFpEF but also the 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 to facilitate systems biology and omics approaches to the pathophysiological mechanisms driving pulmonary vascular remodeling.[58,59] The growing expansion of large deidentified databases with associated biobanks offers an important avenue of investigation to understand how genetic variation and plasma markers are associated 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/noncardiac contributing factors, relevant and reliable animal models need to be selected carefully because many models may resemble only a certain subtype of patients with PH-HFpEF (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–exposed mice have been used to model metabolic syndrome–associated PH and HFpEF.[62] The administration of a high-fat diet to a mouse prone to the 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 high-fat diet–induced PH-HFpEF

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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	Acute increase in afterload does not reflect the pathophysiology of human HFpEF Prolonged banding (after ≈4 wk) leads to LV dilation and systolic HF (HFrEF)
	Leptin-deficient ob/ob mouse	Mouse	No surgery or additional treatment needed	Incomplete characterization of PH-HFpEF in this model
	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
Multihit models	Supracoronary banding+HFD+olanzapine	Rat	Recapitulate many features of human disease Permit 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 (eg, systemic hypertension)

HF indicates heart failure; HFD, high-fat diet; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; and PH-HFpEF, pulmonary hypertension attributable to heart failure with preserved ejection fraction.

and that the disease phenotype is mild in susceptible strains.[64]

Two promising multihit rat models of PH-HFpEF have been developed recently on the basis of the obesity/metabolic phenotype, comorbidities, pulmonary vasculopathy, and inflammation (Table 4). The model with supracoronary aortic banding, a high-fat diet, and olanzapine (an antipsychotic associated with insulin resistance) 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) and obesity in the 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 during treadmill exercise.[67] Because ≈50% to 88% of patients with HFpEF develop exercise-induced PH, even at low-level exercise, this model may serve as an important tool for exploring potential mechanisms and treatment options for exercise-induced PH in HFpEF.[14]

Last, there is an unmet need to develop and use large animal models, which more closely model human physiology and thus may offer more relevant pathophysiological insights. The use of pulmonary vein banding induces severe pulmonary arterial, pulmonary venous, and RV remodeling that has been observed in patients with HFpEF (Table 4).[51,68] The search for an ideal animal model that fits all aspects of the disease remains challenging because of phenotypic heterogeneity and the multifactorial nature of the disease. Through careful definition of specific questions, selection of appropriate fit-for-purpose models (preferably >1 model), 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 about treatment approaches include the following: (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? (3) Should greater consideration be given to the role of RV dysfunction in HFpEF?

Table 5. Selected Recent Clinical Trials Applicable to PH-HFpEF

Acronym, trial number	Intervention	Design	Phase	Target HFpEF population	Primary end point	Comments
Vasodilation						
SERENADE, NCT03153111	Macitentan, 24–52 wk	Multicenter, double blind, randomized, placebo controlled	2b	HFpEF (EF ≥40%), pulmonary vascular disease RV dysfunction	Change in NT-proBNP	Enrichment design; terminated early because of slow enrollment; open-label extension; results pending
SOUTHPAW, NCT03037580	Oral treprostinil, 24 wk	Multicenter, double blind, randomized, placebo controlled	3	HFpEF (EF ≥45%) RHC confirmed WHO group 2 PH	Change in 6MWD	Enrichment design; terminated early because of slow enrollment; open-label extension
HELP-PH-HFpEF[69]	Intravenous levosimendan, 6 wk	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 mm Hg ↓ PCWP from baseline exercise with ≤10% ↓ CI Levosimendan did not reduce exercise PCWP but reduced PCWP incorporating data from rest and exercise and increased 6MWD
DYNAMIC, NCT02744339	Riociguat, 26 wk	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[70]	Inhaled albuterol, acute intervention	Single center, randomized, placebo controlled	2	HFpEF (EF ≥50%) PCWP >15	Change in PVR at 20-W exercise	Albuterol improved exercise PVR compared with placebo (−0.6±0.5 WU vs 0.1±0.7 WU: P=0.003)
Nebivolol, NCT02053246	Nebivolol (β3 agonist), 18 wk	Single center	4	HFpEF (EF ≥45%) mPAP ≥25 mm Hg PCWP ≥15 mm Hg	Change in PVR	Low enrollment
Metabolic						
Metformin for Pulmonary Hypertension HFpEF, NCT03629340	Metformin, 12 wk	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 mo	Multicenter, double blind, randomized, placebo controlled	3	HFpEF (EF ≥40%) Elevated NT-proBNP	Composite: cardiovascular death or HF hospitalization	
DELIVER[72]	Dapagliflozin Event-driven trial	International, double blind, randomized, placebo controlled	3	HFpEF (EF ≥40%) Structural heart disease	Composite: cardiovascular death, HF hospitalization, or urgent HF visit	
PRESERVED-HF, NCT03030235	Dapagliflozin, 12 wk	Multicenter, randomized, double blind, placebo controlled	4	HFpEF (EF ≥45%) Elevated NT-proBNP or BNP	Change in HF-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, during 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

(*Continued*)

Table 5. Continued

Acronym, trial number	Intervention	Design	Phase	Target HFpEF population	Primary end point	Comments
TROPHY II, NCT03611270	PA denervation with a TIVUS system	Multicenter, open label		Cpc-PH HFpEF or HFrEF	Procedure-related adverse events up to 30 d after the procedure	

ASPIRE PH indicates Treatment of Pulmonary Arterial Hypertension Using the Aria CV Pulmonary Hypertension System; BEAT HFpEF, Inhaled Beta-Adrenergic Agonists to Treat Pulmonary Vascular Disease in Heart Failure With Preserved EF; BNP, brain natriuretic peptide; CI, cardiac index; CO, cardiac output; Cpc-PH, combined precapillary and postcapillary pulmonary hypertension; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; DYNAMIC, Pharmacodynamic Effects of Riociguat in Pulmonary Hypertension and Heart Failure With Preserved Ejection Fraction; EF, ejection fraction; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; HELP-PH-HFpEF, Hemodynamic Evaluation of Levosimendan in *PH-HFpEF*; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PH-HFpEF, pulmonary hypertension attributable to heart failure with preserved ejection fraction; PRESERVED-HF, Dapagliflozin in Preserved Ejection Fraction Heart Failure; REBALANCE-HF, Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF; RHC, right-sided heart catheterization; RV, right ventricle; SERENADE, 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; 6MWD, 6-minute walk distance; SOUTHPAW, Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects With Pulmonary Hypertension and Heart Failure With Preserved Ejection Fraction; TPG, transpulmonary gradient; TROPHY II, Treatment of Pulmonary Hypertension Group II Study; WHO, World Health Organization; and WU, Wood units.

Limitations of Prior PH-HFpEF Studies

To date, randomized controlled trials (RCTs) of PH therapies in left-sided heart disease have included both patients with HFpEF and patients with HF with reduced ejection fraction, varied in method of diagnosis of PH, or applied various 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 noninvasive diagnostic criteria. Previously completed and ongoing phase 3 RCTs in HFpEF vary in phenotyping patients, ranging from simple clinical and biomarker phenotyping (eg, EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction]; sodium-glucose cotransporter 2 inhibitors) to Doppler echocardiography in a subset (eg, PARAGON-HF [Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction]; sacubitril/valsartan) to RHC with exercise in all participants (eg, REDUCE LAP-HF II [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]; interatrial shunt device).[71,74,75] Development of a noninvasive diagnostic score that could reasonably differentiate Cpc-PH from Ipc-PH would be valuable. A validated noninvasive score would circumvent the limitation that invasive hemodynamic testing can impose on large, multisite 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, ECGs, 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 and 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 patients with HFpEF, performing phenotyping (eg, biomarkers, echocardiography, invasive hemodynamics, exercise testing), and identifying more homogeneous subtypes such as Cpc-PH that would then be directed toward targeted RCTs. In this way, the RCT is enriched (ie, 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. Last, in adaptive trials, prespecified rules

are incorporated to account for early information from intermediate end points, thereby increasing the 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). In addition, defining appropriate clinical trial end points is important for the successful identification of therapeutic interventions. Primary end points for PH-HFpEF trials may benefit by learning from both prior HFpEF and PAH trials and using a combination of recurrent HF hospitalizations, 6-minute walk distance (6MWD), and Kansas City Cardiomyopathy Questionnaire (Table 5).

Mechanistic Targets in PH-HFpEF

PH-HFpEF is a multifactorial syndrome with a range of disease entities (eg, Ipc-PH, Cpc-PH, and likely others), which creates a conundrum concerning which disease mechanisms to target. Treatment of HFpEF to avoid the 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 of the genetic predisposition to maladaptation of the pulmonary vasculature and extracellular components, which lead to pulmonary vascular remodeling.[82–84] For example, inhaled albuterol (β-agonist) was shown to improve RV-PA coupling, exercise PVR, and left-sided heart filling and therefore may have utility in a PH-HFpEF population.[70] Treatment of pathological changes in the pulmonary veins and treatment of pulmonary endothelial dysfunction represent 2 additional targets.[51]

Role of Patient-Reported Outcomes

The 6th World Symposium on Pulmonary Hypertension highlighted the importance of patient perspectives and patient-reported outcomes, specifically advocating for the inclusion of patient-reported outcomes as secondary end points in RCTs.[85] Given that there are no validated surrogate end points in PH-HFpEF, assessment of patient-reported outcomes 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. Several quality of life measures are validated 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 quality of life or health status, which are important to patients and predictors of prognosis.

Exercise and Potential Role of Digital Health

Supervised exercise programs (eg, 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 the potential role of exercise in patients with PH-HFpEF specifically. Moreover, the mechanisms by which activity interventions improve exercise capacity (eg, skeletal muscle function, cardiopulmonary reserve) 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 attributable to left-sided heart disease have metabolic syndrome.[40] Ranchoux and colleagues[65] demonstrated a link between metabolic syndrome and the development of precapillary PH through activation of interlukin-6–associated pathways in animal models, as well as increased expression of interlukin-6 in lung tissue of patients with PH attributable to left-sided heart disease. Metformin, anti–interlukin-6 antibodies, or other anti-inflammatory agents, along with sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 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 analog, were tested in the SERENADE trial (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) and SOUTHPAW trial (Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects With Pulmonary Hypertension and Heart Failure With Preserved Ejection Fraction), 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 use 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 attributable to left-sided heart disease outside of a clinical trial setting for HFpEF and Cpc-PH.[23]

Augmenting RV Function as a Therapeutic Target

The HELP-PH-HFpEF trial (Hemodynamic Evaluation of Levosimendan in PH-HFpEF) used an approach similar to that in SERENADE and SOUTHPAW but enrolled patients with invasive hemodynamic evidence of PH-HFpEF and 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 mm Hg, which was required for subsequent randomization to levosimendan versus placebo.[93–95] Although it did not meet its primary end point of lowering exercise PAWP, levosimendan was associated with a 30-m placebo-corrected increase in 6MWD and had favorable hemodynamic effects, thereby supporting the novel trial design as a potential blueprint for future RCTs.[69]

Targeting the RV with treatments such as levosimendan is of potential utility in patients with PH-HFpEF with RV dysfunction by increasing unstressed blood volume and thereby limiting excessive splanchnic vasoconstriction and stressed blood volume delivery to the sick right side of the heart in these patients.[96] Myotropes (eg, 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

Last, 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 (Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF) could provide insight into patients with PH-HFpEF and Cpc-PH. Improving splanchnic venous capacitance increases unstressed blood volume and decreases stressed blood volume. Increased stressed blood volume is an important pathophysiological factor in HFpEF, particularly in obesity-related HFpEF, because it has been shown to affect 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 patients with PH-HFpEF in whom proximal PA stiffening is a major problem and more common than distal PA stiffening. Last, PA denervation improves PVR and increases 6MWD in patients with PAH and may be effective in patients with PH-HFpEF.

CONCLUSIONS

PH-HFpEF is a growing epidemic with high morbidity and 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.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Writing Group Disclosures

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*Modest.

†Significant.

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Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
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*Modest.

†Significant.

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