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Pulmonary Hypertension in Heart Failure Preserved Ejection Fraction Prevalence, Pathophysiology, and Clinical Perspectives

Marco Guazzi, MD, PhD

An elevation of left ventricular diastolic and pulmonary venous pressure is typical of heart failure (HF) regardless of left ventricular (LV) ejection fraction. Normal left ventricular diastolic function keeps both pressures low (<12 mmHg), although some increase may be observed during stress conditions, such as volume overload¹ and exercise.² When these changes occur within a range of transient periods and in a normal heart, they are well tolerated because of the pulmonary vasculature ability to recruit and distend the capillary network.³

Heart failure with preserved ejection fraction (HFpEF) is a condition presenting, by definition, with an impaired relaxation and stiffened myocardium, which is in part consequence of an increased load to the left ventricle attributable to the stiff arterial system and resulting in a well-defined ventricular-vascular uncoupling. These main hemodynamic alterations expose the lung vasculature to pressure-induced challenges whose most immediate acute threat is pulmonary edema.⁴ In the long term, the sustained backward hemodynamic transmission, along with the potential contribution of mitral insufficiency, increases the pulsatile loading on the right ventricle (RV)⁵ and triggers pulmonary hypertension (PH) development and symptom exacerbation.⁶ Thus, as a consequence of hemodynamic and functional perturbations, PH-HFpEF develops as a more advanced corollary of diastolic HF, leading to abnormal phenotypes of the lung microcirculation,^{7,8} the arterial system, and right heart function⁹⁻¹¹ (Figure 1).

Recent reports have highlighted PH-HFpEF as a condition more frequent than previously appreciated and, during the last few years, some investigators have then succeeded to define the prevalence¹²⁻¹⁴ and the hemodynamic patterns accompanying the syndrome,¹⁴⁻¹⁶ providing the basis for a more focused search of left-sided PH preventive and therapeutic strategies.

Definition, Epidemiological Data, and Diagnosis

Left-sided PH, or Group 2, is defined as an increase in mean pulmonary artery pressure (PAP) >25 mmHg at rest secondary to an elevation in pulmonary capillary wedge pressure (PCWP) ≥15 mmHg, which is the peculiar hemodynamic pattern of left-sided PH compared with other forms of PH. Potential coexistence of mitral insufficiency is the other distinctive feature that differentiates cardiac PH. There is evidence that mitral

insufficiency although more frequent in HF reduced ejection fraction (HFrEF) may also occur in HFpEF.^{17,18} Although the definition is universal, the clinical PH phenotype that is associated with HFpEF may be variable, considering that PH may set in acute HF or chronic HF. In acute HF, it may develop in acutely developing (de novo) or chronic acutely exacerbating HF (on CHF) as a first clinical manifestation or superimposed. In chronic HF, PH may be part of the clinical scenario at different stages (C to D) in stable or unstable hemodynamic conditions (Figure 2). When PH develops in chronic conditions, its clinical significance is tightly linked to the disease severity.

By virtue, PH-HFpEF is referred and has been only approached as the chronic condition that primarily involves elderly patients with multiple comorbid disorders, becoming the main reason for hospitalization and clinical deterioration.^{15,16,19-21} Nonetheless, persistence of some degree of PH after acute hospital admission drives a worse clinical outcome and may represent a basic target of treatment.²²

Compared with PH attributable to HFrEF more pathogeneses account for PH-HFpEF with a high prevalence of hypertensive heart disease, diabetes mellitus, and obesity.²³

Epidemiological studies have documented that PH in HFpEF is highly prevalent irrespective of different case-series and methods for PAP determination and PH diagnosis (invasive versus estimated pulmonary hemodynamics). This condition is much more common than other, more investigated, forms of pulmonary arterial hypertension and, according to most recent Registries,¹³ it is more prevalent than left-sided PH because of HFrEF, sharing a similar hemodynamic pattern and clinical course. In the New York Heart Failure Registry, among 619 recently hospitalized patients with HFpEF, PH of moderate entity (average RV systolic pressure, 46 mmHg) was detected in 44% of cases.²⁴ Data from Olmsted County database obtained by Doppler echocardiography show a PH rate that may be ≈80% when systemic hypertension is the main underlying cause.¹² Observational studies performed in a wide cohort of patients with HFpEF with several comorbid diseases and multiple risk factors have shown a 53% PH prevalence, as assessed by right heart catheterization.^{25,26}

In the recently published Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial,²⁷ Doppler evidence of PH was observed in

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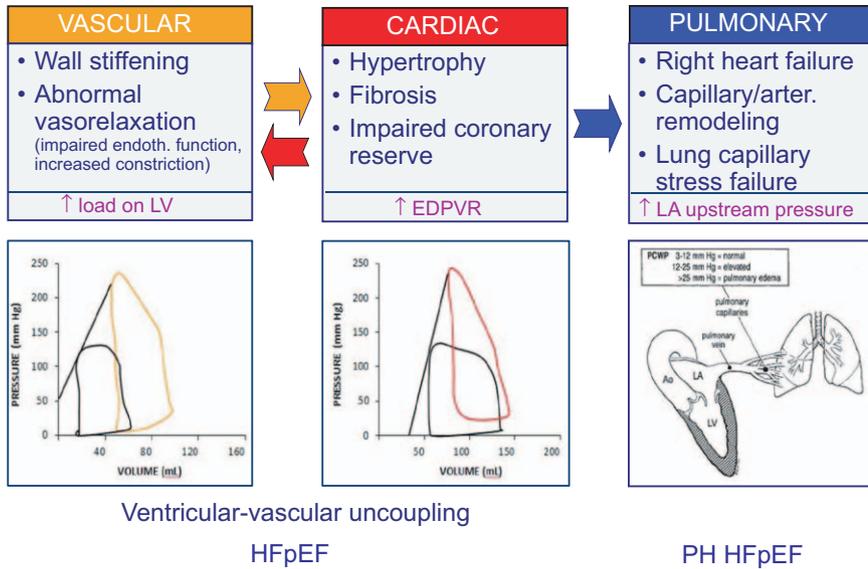


Figure 1. From heart failure with preserved ejection fraction (HFpEF) to pulmonary hypertension (PH) HFpEF: hemodynamic components and pathophysiological correlates. In HFpEF, the central pathophysiological role is played by an impaired left ventricle (LV) filling mechanics that can arise both from intrinsic structural and molecular alterations in the LV (stiff heart) secondary to myocyte hypertrophy, fibrosis, and impaired coronary reserve and as a consequence of an increased load to the heart imposed by the stiff arterial system, which leads to a well-defined derangement of the ventricular arterial unit. Whatever the predominant cause is, ventricular or vascular, this uncoupling generates the pathophysiological bases for a third hemodynamic component that is the upstream increase in left atrial pressure with hemodynamic involvement of the pulmonary circulation. This generates the PH-HFpEF syndrome that is characterized by a cascade of

events leading to lung capillaries stress failure, subsequent arterial system remodeling, and RV dysfunction and failure. PH-HFpEF is a consequence rather than a cause of the disease that can become relevant in terms of symptoms exacerbation and clinical evolution. Growing recent studies have pointed out the syndrome of PH-HFpEF as an evolving stage of diastolic HF that seems more frequent and clinically meaningful than previously thought. EDPVR indicates end-diastolic pressure–volume relationship; and LA, left atrium.

36% of cases. Collectively, the expected rate of PH in the wide variety of HFpEF phenotypes can be ≈50%.

Whereas in HFrEF a distinctive feature is LV enlargement and loss of function, in PH-HFpEF, the preserved EF and, in some instance, morphological characteristics of the LV may generate some overlap with the phenotype of pulmonary arterial hypertension (PAH). This may happen especially when clinical presentation is similar despite important clinical clues that may differentiate the 2 conditions, such as the presence of left atrial enlargement, left ventricular hypertrophy (LVH), and the finding of subclinical pulmonary edema on chest radiograph. In this regard, it is helpful to follow the algorithm proposed by the task force of the 4th WHO Symposium at the Dana Point (Figure 3).²⁸ What it suggested is that patients with dyspnea and

Echo diagnosis of preserved EF can be allocated in 3 different groups. There is a small group of patients in whom, despite normal EF, a diagnosis of PH-HFpEF is unlikely, because they are young with no comorbidities, having chest radiograph findings typical and drug use specific of PAH. Then, there is the group of patients, the vast majority, in whom it is easy to define a PH-HFpEF picture. They exhibit all the demographic and clinical characteristics typically described in population-based trials, such as old age with a constellation of cardiovascular risk factors, LVH, and atrial enlargement at echo, RX findings of HF and increased natriuretic peptide levels. Finally, there is a minority whose diagnosis is uncertain, because they have any age, are euolemic with no or mild hypertension and few comorbid risk factors, and LVH is not clearly detectable at echocardiography. This is the subset of patients that need right heart characterization (RHC) to define whether they definitively have PAH, PH-HFpEF, or mixed forms. RHC is useful because it helps to better stratify to pure diastolic component as cause of PH (PCWP≥15 mmHg and pulmonary vascular resistance [PVR] within normal limits), primarily PAH when PVR≥3 wood/unit and PCWP<15 mmHg or the condition with increased PVR≥3 wood/unit and elevated PWCP. This condition may be challenged with pharmacological agents and results into a reduction in PCWP and not of PVR or both, suggestive of PAH and HFpEF, respectively.

Recent observational studies have clarified the population characteristics of PH-HFpEF. Thenappan et al¹⁴ found that for similar mean PAP elevation, right ventricular hypertrophy, and right atrial enlargement, these patients were older, had a higher prevalence of cardiovascular comorbidities, worse exercise capacity and renal function, and often had left atrial enlargement compared with patients with idiopathic PAH. Compared with HFpEF without PH, a higher portion of patients with PH-HFpEF was female, and RV geometry was indicative of RV enlargement and hypertrophy. These changes were similar to those observed in PAH. In the study by Leung

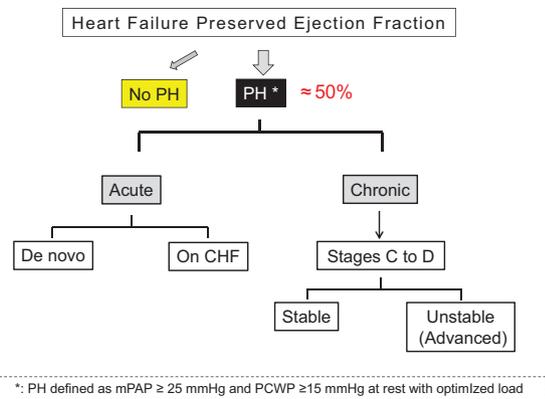


Figure 2. Different clinical conditions associated with pulmonary hypertension–heart failure with preserved ejection fraction (PH-HFpEF). It is estimated that ≈50% of patients with HFpEF develop PH, and this may occur in the presence of different clinical conditions. In acute HF, PH may be a manifestation of a de novo or on CHF. In chronic HF (CHF), PH occurs in different stages (from C to D) and hemodynamic conditions (stable vs unstable). mPAP indicates mean pulmonary pressure; and PCWP, pulmonary capillary wedge pressure.

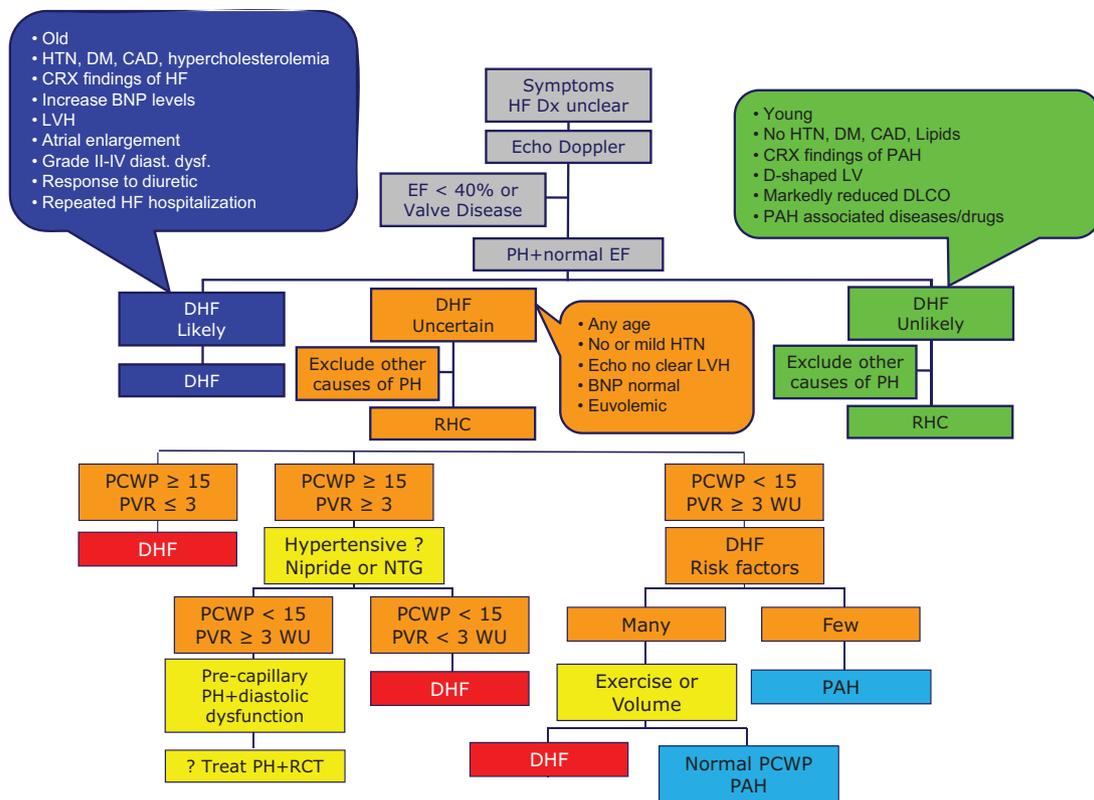


Figure 3. Diagnostic algorithm for pulmonary hypertension–heart failure with preserved ejection fraction (PH-HFpEF) proposed by the working group on non–pulmonary arterial hypertension (PAH)-PH at the 4th World Symposium on PH (Dana Point).²⁸ Patients with dyspnea having a normal EF and PH diagnosed with Echo may be allocated in 3 different groups. A small group of patients in whom despite normal EF, eventually a diagnosis of PH-HFpEF is unlikely because they are young with no comorbidities, they have chest radiograph typical PAH findings and use of specific PAH drugs (green). There is a group of patients, the vast majority, in whom it is easy to define a PH-HFpEF picture, because they exhibit all the demographic and clinical characteristics typically described in population-based trials such as elderly with a constellation of cardiovascular risk factors, left ventricular hypertrophy (LVH), and atrial enlargement, chest radiograph findings of HF and increased natriuretic peptide levels (blue). Finally, there is a minority whose diagnosis may be challenging because they have any age, are euvolemic with no or mild hypertension (HTN) and few comorbid risk factors, and LVH is uncertain at echocardiography. This is the subset of patients that need right heart catheterization (RHC) to define whether they definitively have PAH, PH-HFpEF, or mixed forms. RHC is useful to better stratify to pure diastolic component as a cause of PH (pulmonary capillary wedge pressure [PCWP]≥15 mmHg and pulmonary vascular resistances [PVR] within normal limits), primarily PAH when PVR ≥3 wood/unit (WU) and PCWP < 15 mmHg, or the condition with increased PVR ≥3 WU and elevated PCWP. This condition may be challenged with pharmacological agents and results in a clear reduction in PCWP and not of PVR or a decrease of both, suggestive of PAH and HFpEF, respectively. BNP indicates brain natriuretic peptide; CAD, coronary artery disease; CRX, chest radiograph; DHF, diastolic heart failure; DLCO, lung diffusing capacity for carbon monoxide; DM, diabetes mellitus; and NTG, nitroglycerine. Reprinted from Hoepfer et al²⁸ with permission of the publisher. Copyright © 2009, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

et al,²⁶ PH-HFpEF patients had higher LV end-diastolic pressure (>25 mmHg), more frequently also had advanced age (>80 years) and presented with obesity, atrial arrhythmia, and chronic obstructive pulmonary disease compared with HFpEF.

Pulmonary Vascular Disease and Hemodynamics

Insights into pulmonary vascular alterations and function in HFpEF have long been missing, because of a lack of appreciation on the chronic effects of a sustained increase in left atrial pressure on the pulmonary vasculature. Especially, major pathways that may be involved in the pathobiological changes of lung arterial system are unknown to a large extent, and their investigation may pave the way for novel and specific therapeutic targets.

When left atrial pressure is increased, 2 major vascular modifications occur. The first is a stress failure of the capillaries

and alveolar membrane, manifesting as a typical acute phenomenon induced by barotrauma injury of lung microvessels, which disrupts endothelial function and permeability and impairs the biological and functional properties of the alveolar unit (gas exchange and fluid filtration and reabsorption). Overt pulmonary edema is the significant clinical correlate of capillary stress failure. Edema activates metalloproteinases, causing degradation of matrix proteoglycans and alteration in the composition of unit membrane. The other observed phenomenon is a true remodeling process that is linked to sustained pressure injury with time and involves capillaries and especially the wall of small arteries. Remodeling is triggered by the release and complex interplay of local hormonal (angiotensin II and endothelin 1) and inflammatory (tumor necrosis factor-α) mediators that generate a reactive response in the inner and media wall of the vessels with excessive collagen type IV deposition in the extracellular matrix and changes

in the geometry and function of the alveolar-capillary membrane. Genetic factors may likely influence these pulmonary vascular structural changes, although a clear putative role and identification have not been reported. Endothelial dysfunction is predominant in mediating the impaired pulmonary vascular smooth muscle relaxation that plays an integral role in the functional alterations of the pulmonary vasculature.

Whereas acute stress failure is a reversible phenomenon, reversibility of lung vascular remodeling is uncertain.⁷

Animal studies have brought some relevant information on the development and transition from failure to remodeling in left-sided PH and especially PH-HFpEF. In a mouse model of LVH, increased left atrial pressure and development of PH attributable to transaortic constriction, massive lung fibrosis, leukocyte infiltration, and profound vascular remodeling have been observed after 4 weeks. Interestingly, associated with severe LV diastolic dysfunction, there was a significant increase of lung weight that was not merely the result of an increase of lung water, but rather the consequence of intrinsic tissue and vascular changes.⁸ Additional findings obtained in a similar experimental model were a clear stress failure of small capillaries and alveoli²⁹ and a peculiar scenario of endothelial dysfunction caused by singular impairment of endothelial [Ca(2+)](i) homeostasis and signaling, characterized by a lack of [Ca(2+)](i) oscillations and deficient or attenuated [Ca(2+)](i) responses to mechanical or chemical stress with histamine, acetylcholine, or thapsigargin.³⁰

The significance of these findings in humans is still under scrutiny, and a severity-related definition of molecular and cellular pathways implicated in the capillary lung disease seems to be a missing step for knowledge advancement on left-sided PH consequences and their role in the progression of the disease.

Hemodynamic Stages

Pulmonary hemodynamic stages have been classically categorized under passive and reactive phenotypes irrespective of LVEF. In both cases, mean mPAP must be ≥ 25 mmHg at rest.³¹ In the passive condition, the increase in pulmonary pressures arises solely from increased LV filling pressure and left atrial pressure in the absence of any increase in the transpulmonary gradient (TPG), and at least apparently no component of PH is derived from abnormalities intrinsic to the pulmonary vascular system.⁶ This condition is generally considered to be reversible, although a true definition of the pathobiological changes occurring at this stage is missing. There is the intriguing recent demonstration obtained in patients with HFpEF that some degree of capillary remodeling may occur even at this stage, thus challenging the paradigm.³²

Reactive PH is the consequence of a sustained increase in left atrial pressure, that definitively leads to characteristic pathological changes in the distal pulmonary arteries and arterioles,³³ resulting in an abnormal increase in transpulmonary pressure gradient. In agreement with this concept, the reactive hemodynamic pattern may develop as out of proportion, which practically means rise in pulmonary pressures greater than expected for that given increase in PCWP. At this stage, vascular injury may be fixed or reversible. There may be an interindividual variability in the time course and extent of both development and regression of the obstructive changes

observed in group 2 PH, which is likely linked to constitutional factors without demonstration of any genetic predisposition.

Some considerations are important on how to define the TPG, and whether or not is indeed reflective of a constitutive vascular component. Specifically the definition of TPG (difference between mean PAP and PCWP) that becomes significant for a limit ≥ 12 mmHg has been questioned and, according to what has been originally proposed by Harvey et al,³⁴ the use of the diastolic pressure gradient (DPG, difference between diastolic PAP and PCWP) is now preferred, based on the main concept that the gradient between mean PAP and PCWP is sensitive to changes in cardiac output and load conditions especially related to the pulsatile load.³⁵ The dominant concept behind this is that the pulmonary flow is maximum during systole and negligible at end diastole and in a normal population diastolic PAP is approximately equal to the pressure in the left atrium. Yet, both recruitment and distension of the pulmonary vessel decrease the backward transmission of left atrial pressure. By applying these concepts, Gerges et al³² have retrospectively assessed the prognostic significance of the DPG in a population of patients with HFpEF, showing that in cases with postcapillary PH and a TPG >12 mmHg, a worse median survival was associated with a DPG ≥ 7 mmHg compared with a DPG <7 mmHg (101 months, $P=0.010$). The main survival curve separation, however, was observed between the non-PH versus passive PH group rather than passive versus precapillary PH. Nonetheless, the elevated DPG (≥ 7 mmHg) was associated with more advanced pulmonary vascular remodeling. The definitive clinical and prognostic implications of using a DPG classification remain to be elucidated, especially considering that an extensive analysis³⁶ on the prognostic significance of DPG performed in >5000 patients with Group 2 PH has shown a lack of any prognostic discriminatory power when event-free survival was analyzed according to different DPG cutoff. In this analysis, patients with lower DPG unexpectedly showed the highest PCWP values.

Interestingly enough, in a recent study involving a group of patients with HFpEF of different severity, a significant correlation was found between the degree of TPG and pulmonary vascular resistance with the degree of LV myocardial extracellular matrix accumulation assessed by both cardiac magnetic resonance T1 mapping analysis and biopsy tissue analysis.³⁷

RV Dysfunction and Failure

Once precapillary PH is established, the obstructive effects on the pulmonary arteries and increase in PAP lead to an increase of the RV afterload. In the face of this, RV adapts to maintain output, primarily by the development of hypertrophy and eventually, if the overload persists, of dilatation, tricuspid regurgitation, loss of contractility (by muscle mass unit), and an irreversible decrease in RV function may follow.³⁸ RV dysfunction and tricuspid regurgitation further complicate HF syndrome by central venous pressure elevation, which affects the release of natriuretic peptides, impairs renal function, definitively causing congestion and a high degree of neural and hormonal activation.³⁸ Renal dysfunction and renal associated mortality seem to be higher in HFpEF compared with HFpEF.³⁹ Although, together with PH, the development

of RV dysfunction is known to be among the most significant modifiers of both the natural history and prognosis of patients with HFrEF,⁶ the extent and clinical significance of RV failure and the extent of chamber remodeling development in HFpEF is increasingly recognized and studied.⁶ Studies investigating the pattern of right heart function and geometry in PH-HFpEF are summarized in Table 1.^{9–11,14,15,21,40–45}

In a report by Puwanant et al,¹¹ RV dysfunction, assessed by RV fractional area and tissue Doppler S prime, was not uncommon in patients with HFpEF although in a milder degree compared with HFrEF. Similar findings were reported

by looking at RV global longitudinal early diastolic strain rate and systolic RV global longitudinal systolic strain.¹⁰

In a larger population of PH-HFpEF, Damy et al⁹ confirmed an RV dysfunction rate of 50% of cases. Although the prevalence of a severely compromised RV function (tricuspid annular plane systolic excursion, TAPSE <14 mm) was lower in patients with HFpEF than in patients with HFrEF (19% versus 39%), a similar prediction power was found for the lower TAPSE irrespective of systolic or diastolic origin of left-sided PH. In a recent study by our group,⁴³ we studied the RV contractile function in a mixed HFpEF and HFrEF

Table 1. Studies Investigating Right Heart Function and Geometry Changes in PH-HFpEF Compared With HFpEF and No PH, Asymptomatic LV Diastolic Dysfunction, HFrEF, and Patients With PAH

Studies	Patients,n/Types of HF	Right Heart Function	Right Heart Geometry	Prognostic Significance of RV Dysfunction
Damy et al. <i>J Cardiac Fail</i> , 2012 ⁹	309 PH-HFpEF vs 722 HFrEF and 516 controls	TAPSE↓ but significantly higher than HFrEF	Right atrial volume index AVI↑	TAPSE prognostic especially in patients with TAPSE <14 mm
Puwanant et al. <i>Eur J Echocardi</i> , 2009 ¹¹	51 HFpEF vs 49 HFrEF	RVFA↓, TDI S ₁ ↓, TAPSE↓ but significantly higher than HFrEF
Thenappan et al. <i>Circ Heart Failure</i> , 2011 ¹⁴	100 PH-HFpEF vs 522 PAH and 45 HFpEF	...	Right atrial size↑ vs HFpEF RV hypertrophy↑ vs HFpEF (P<0.001)	...
Anjan et al. <i>Am J Cardiol</i> , 2012 ¹⁵	113 PH-HFpEF Group with BNP>100 pg/dL vs PH-HFpEF Group with BNP<100 pg/dL	PH-HFpEF Group with BNP> 100 pg/dL RVFA change↓, TAPSE↓ compared with PH-HFpEF Group with BNP < 100 pg/dL (P<0.001 all)	PH-HFpEF Group with BNP> 100 pg/dL RV wall thickness↑, Right atrial area index ↑, RV end-systolic and end-diastolic area ↑ (all P<0.001)	...
Guazzi et al. <i>Circulation</i> , 2011 ⁴⁰	44 PH-HFpEF	TAPSE↓, MSEJR↓	RV maximal short axis↑	...
Morris et al. <i>J Am Soc Echocardi</i> , 2011 ¹⁰	201 PH-HFpEF vs 364 asymptomatic LV diastolic dysfunction	RV global longitudinal systolic strain↓	RV wall thickness↑, RV basal, midcavitary diameter, and longitudinal dimensions ↑(P<0.001 all)	...
Mohammed et al. <i>Circulation</i> [abstr], 2011 ⁴¹	548 HFpEF with variable degrees of PH	TAPSE↓ progressively according to a combined PASP stratification	...	Highly prognostic role of RV dysfunction combined with PASP>47 mmHg
Agarwal et al. <i>J Heart and Lung Transpl</i> , 2012 ²¹	339 patients with HFpEF	RV function (qualitative assessment)↓: -mild dysfunction in 15.9% -moderate dysfunction in 19.8% -severe in 18%	RA size↑ in 63% of cases (qualitative assessment)	...
Rabinovitz et al. <i>J Cardiac Fail</i> , 2013 ⁴²	635 PH-HFpEF	RV function (qualitative assessment)↓ especially in patients who are hyponatremic
Guazzi et al. <i>Am J Physiol</i> , 2013 ⁴³	46 HFpEF with different degrees of PH vs 247 HFrEF	TAPSE↓ at the same extent as HFrEF. Similar TAPSE distribution across PASP relationship
Burke et al. <i>Circ Heart Fail</i> , 2014 ⁴⁴	419 patients with different degrees of PASP	TAPSE ↓ in 28%, RVFAC↓ in 15%	35% with RV hypertrophy	RV wall thickness most predictive of worse outcome
Melenovsky et al. <i>Circulation</i> [abstr], 2013 ⁴⁵	41 PH-HFpEF vs 45 HFpEF	RVFAC↓ in PH-HFpEF	RA and RV size↑ in PH-HFpEF	Highly prognostic role of RVFAC

AVI indicates atrial volume index; BNP, brain natriuretic peptide; HF, heart failure; HFrEF, HF reduced ejection fraction; MSEJR, mean systolic ejection rate; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PH-HFpEF, pulmonary hypertension–HF preserved ejection fraction; RAVI, right atrial volume index; RV, right ventricle; RVFAC, RV fractional area; TAPSE, tricuspid annular plane systolic excursion; and TDI S₁, tissue Doppler systolic component.

population by plotting the relationship between TAPSE, as an index of fiber shortening versus pulmonary arterial systolic pressure (PASP), as an indicator of developed force and proposing this relationship as an *in vivo* noninvasive, easy-to-obtain index of length/force relationship. As shown in Figure 4, the overall RV contractile performance was similarly distributed across the regression line in both populations, suggesting that the RV may be similarly exposed to variable loads irrespective of the quality of LV systolic dysfunction.

In a prospective analysis of 419 patients with HFpEF, a reduced LV compliance and RV adverse remodeling were the only 2 predictors of worse outcome.⁴⁴

Data from Mohammed et al,⁴¹ obtained in 548 subjects with HFpEF with variable degree of PH and RV involvement, documented a worse prognosis for patients with PASP above the median (>47 mmHg) and RV systolic dysfunction. Interestingly, RV systolic dysfunction was a significant predictor of mortality even after adjustment for age and PASP in a Cox regression model (Hazard Ratio=1.4, $P=0.02$; Figure 5). Further evidence has recently been brought by Melenovsky et al⁴⁵ reporting a worse RV function and prognosis in PH-HFpEF associated with atrial fibrillation.

PH Phenotypes and Clinical Studies

Giving the increasing referral number of patients with PH-HFpEF to tertiary centers, the precise definition and staging of clinical phenotypes and prognostic-related features in this subset of patients remain a priority. As elegantly proposed by Shah⁴⁶ (Figure 6), 3 different HFpEF phenotypes can be identified: phenotype A, that is the most frequent and presents with initial diastolic dysfunction and exercise-induced filling impairment (ie, exercise-induced rise in LV filling pressure), but few symptoms at rest; phenotype B, characterized by evident signs and symptoms of HF (NYHA class III), chronic

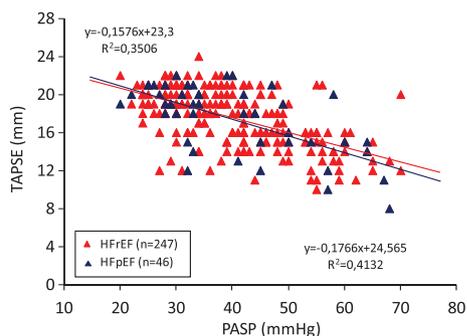


Figure 4. Plot of tricuspid annular peak systolic excursion (TAPSE)/pulmonary arterial systolic pressure (PASP) relationship according to heart failure reduced ejection fraction (HFpEF; $n=247$, red symbols) vs HF preserved ejection fraction (HFpEF; $n=46$, blue symbols).⁴³ The overall right ventricular (RV) performance relationship was similar in both groups, and both HFpEF and HFpEF were homogeneously distributed across the relationship, suggesting that a similar degree of RV dysfunction may occur irrespective of left ventricular morphological characteristics and predominance of systolic or diastolic dysfunction. Reprinted from Guazzi et al⁴³ with permission of the publisher. Copyright © 2013, The American Physiological Society. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

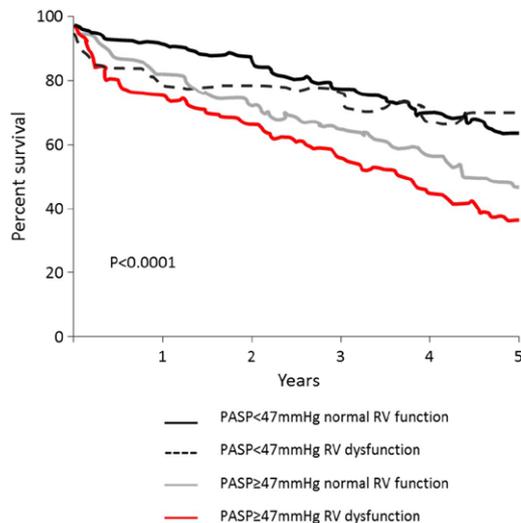


Figure 5. Five-year Kaplan–Meier survival curves in heart failure preserved ejection fraction according to pulmonary arterial systolic pressure (PASP) median value distribution (47 mmHg) and right ventricular (RV) function (normal or systolic dysfunction). Reprinted from Mohammed et al⁴¹ with permission of the publisher. Copyright © 2011, Wolters Kluwer Health, Lippincott Williams & Wilkins. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

volume overload, and detection of initial PH, and phenotype C associated with PH and overt right HF. Although each phenotype can be classified as having HFpEF, the 3 conditions represent distinct stages of the HFpEF syndrome. The proposed subdivision has relevant implications and may provide a strong rationale and generate new working hypotheses for matching the best drug to the right patient. Also, it can be adopted for orienting to experienced centers the PH evolving phenotype.

Development of PH is a well-established precipitating factor for poor outcome¹² with a 2- to 3-fold increase in the risk when it combines with depressed RV function.⁴⁰

The risk related to PH-HFpEF has been analyzed under a score format,²¹ which was validated in 2 independent PH-HFpEF cohorts including a retrospective and a prospective systemic cohort. Several clinical characteristics emerged as relevant and independent predictors of all-cause death with 8 variables (NYHA class, diastolic blood pressure, pulmonary artery saturation, interstitial lung disease, hypotension, RV hypertrophy, DLCO, and creatinine) identified as combined prognosticators at multistep regression analysis.

Additional recent observations suggest that the severity and prognosis of the disease may differ according to brain natriuretic peptide (BNP) levels with a more severe PH presentation when $BNP \geq 100$ pg/dL.¹⁵ An analysis performed by Rabinovitz et al⁴² in 635 patients with PH-HFpEF, hyponatremia was associated with a 82% increased risk of mortality levels compared with patients with normal blood sodium levels, and the mortality risk of those with concomitant RV dysfunction was >2-fold even after adjustment for clinical, echocardiographic, and laboratory variables. These interesting findings await further evidence, but open further scenarios in the characterization, risk stratification, and potential clinical decision-making of PH-HFpEF. Available data regarding

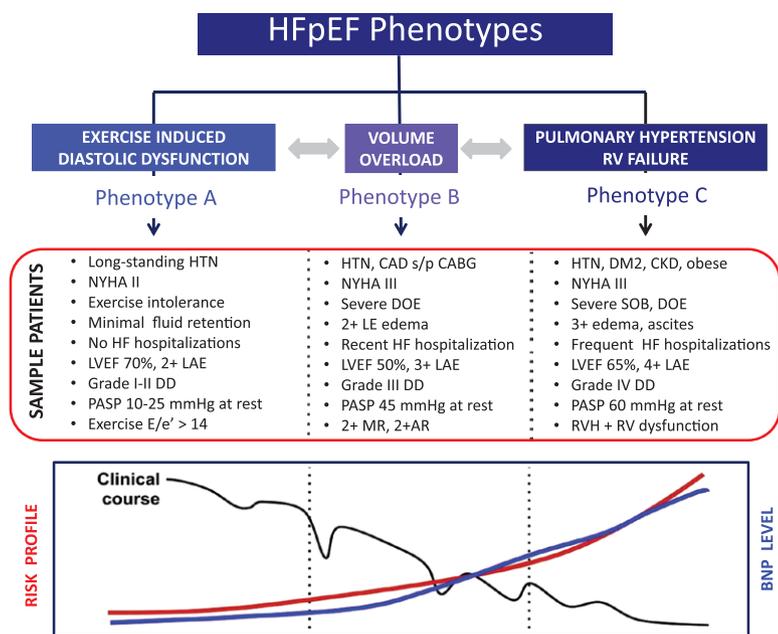


Figure 6. Different heart failure preserved ejection fraction (HFpEF) phenotypes based on clinical signs and symptoms, degree of diastolic dysfunction, and presence or not of pulmonary hypertension (PH) and right heart disease.⁴⁶ Phenotype A is relatively frequent and associated with few symptoms at rest, initial diastolic dysfunction and exercise-induced left ventricular (LV) filling impairment. Phenotype B is characterized by evident signs and symptoms of HF (New York Heart Association class III), chronic volume overload and mild to moderate PH at rest. Phenotype C is associated with severe PH at rest and overt right heart failure. AR indicates aortic regurgitation; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; DD, diastolic dysfunction; DM2, diabetes mellitus type 2; DOE, dyspnea on exertion; E/e' , ratio of early mitral inflow to early mitral annular diastolic tissue velocity; HTN, hypertension; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary arterial systolic pressure; RVH, right ventricular hypertrophy; and SOB, shortness of breath. Reprinted from Shah⁴⁶ with permission of the publisher. Copyright © 2013, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

passive and mixed PH subgroups are variable and limited by small- to medium-sized single center case-series, incomplete characterization of left and right ventricular function, and valve heart disease. Table 2 reports the studies^{14,15,26,40,47,48} that have assessed PH-HFpEF by right heart catheterization. For similar levels of hemodynamic dysfunction as assessed by mean PAP and PCWP, studies invariably document different PH stages according to hemodynamic classification. All studies, except one, report an increase in TPG with a corresponding increase in DPG in 3 of those, implying a rate of reactive out of proportion PH, which clearly suggests functional and structural involvement of the pulmonary arterioles. Notably, despite similar mPAP levels, discrepancies among studies are consistent with an intrinsic variability in the evolving natural process of the disease, further emphasizing that the biological rather than the hemodynamic staging may indicate some intriguing directions toward targets of treatment.

An additional population that is increasingly studied is the group of elderly patients who experience exertional dyspnea with normal echocardiographic findings and pulmonary

hemodynamics at rest. In some of these patients, exercise may become an important challenge by inducing elevated PCWP and PH, suggesting that their symptoms may mirror an early stage of PH-HFpEF. Indeed, in a well-selected population of 55 such patients without PH at rest with a BNP assay within normal range and in stable hemodynamic conditions, Borlaug et al⁴⁹ found that exercise testing induced a consensual PCWP and end-diastolic pressure elevation in ≈50% of subjects. Similar observations were reproduced by Maeder et al.⁵⁰ Furthermore, Shim et al⁵¹ found that patients with HFpEF who had exercise-induced PH in the presence of elevated E/e' had a higher rate of hospitalization or mortality. Like PH at rest, exercise-induced PH is not specific to HFpEF. Thus, exercise testing with hemodynamic monitoring may be a useful mean to uncover latent and early PH-HFpEF, and a new algorithm has recently been proposed.⁵²

Therapeutic Perspectives

There are currently no consensus therapeutic strategies and reference algorithms for group 2 PH except for advanced

Table 2. Studies Assessing Pulmonary Hemodynamics Phenotypes in PH-HFpEF

Studies	Patients, n	Rest mPAP, mm Hg	Rest PCWP, mm Hg	TPG, mm Hg*	DPG, mm Hg†
Leung et al. <i>Am J Cardiol</i> , 2010 ²⁶	239	34.2	21.8	>12	0.4
Guazzi et al. <i>Circulation</i> , 2011 ⁴⁰	44	39	22	>12	9.4
Thenappan et al. <i>Circ Heart Fail</i> , 2011 ¹⁴	100	49	23	>12	...
Agarwal et al. <i>J Heart and Lung Transpl</i> , 2012 ²¹	339	43	20	>20	...
Afshar et al. <i>Op Card Med J</i> , 2012 ⁴⁷	50	37.4	25.5	26	...
Anjan et al. <i>Am J Cardiol</i> , 2012 ¹⁵	159	35	26	9	2
Adir Y et al. <i>Respiration</i> , 2013 ⁴⁸	20	>12	6.3

DPG indicates diastolic pulmonary gradient; mPAP, mean pulmonary pressure; PCWP, pulmonary capillary wedge pressure; PH-HFpEF pulmonary hypertension-HF preserved ejection fraction; and TPG, transpulmonary gradient.

*mPAP-PCWP.

†diastolic PAP-PCWP.

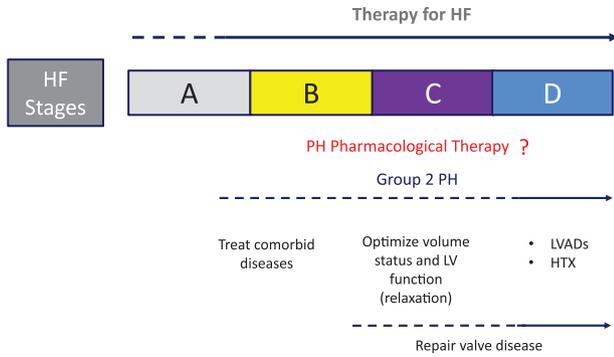


Figure 7. Current therapeutic strategies for reversing/treating pulmonary hypertension (PH) in left heart disease. Guidelines suggest treatment of comorbid disorders, optimization of volume status, and improvement of left ventricular (LV) relaxation properties as mainstay interventions unless correction of valve disease (primarily mitral insufficiency), LV assist devices (LVAD), and heart transplantation (HTX) are indicated. Whether pharmacological treatment of pulmonary vascular disease may be a conceivable goal that may favorably impact the course of the disease remains a challenging open question. HF indicates heart failure.

stages of the disease, when mechanical pump support and heart transplantation are needed. Specifically, no evidence is provided on preventing and reversing early or intermediate stages of PH except for treating comorbid disorders and optimizing volume status and LV relaxation properties (Figure 7).

The obvious and compelling need to consider the lung vascular disease a primary therapeutic target in patients with PH-HFpEF seems intriguing but remains questionable because of few evidences available at this time. An explanation may be that endothelin receptor antagonists (ERAs) and prostanoids, which are effective treatments for PAH, have been shown to be neutral or even harmful in patients with left-sided PH.⁶ Accordingly, despite their use in cardiac forms of PH being contraindicated, there are 2 provocative ongoing trials aimed at testing the potential significance of ERAs in PH-HFpEF. These studies may challenge this scenario based on some

different and still unproven rationale in the context of HFpEF associated with PH. The Safety and Efficacy Trial to Treat Diastolic Heart Failure Using Ambrisentan (ClinicalTrials.gov Identifier: NCT00840463) will have as primary end point the safety of Ambrisentan at 16 weeks, and as secondary end point WHO functional class, 6-minute walk test distance and 36-Item Short Form Health Survey Scores. The other trial is Safety and Efficacy of Bosentan in Patients With Diastolic Heart Failure and Secondary Pulmonary Hypertension (BADDHY; ClinicalTrials.gov Identifier: NCT00820352) and is planned to look at the effects of 12 weeks of bosentan on 6-minute walk test distance and quality of life.

At variance with other pulmonary vasodilators, evidence is accumulating that inhibition of phosphodiesterase-5 (PDE5), the isoenzyme that breaks down cGMP to its inactive form, may be an effective and well-tolerated tool for targeting the pulmonary vasculature and unloading the RV in left-sided PH.⁵³ This is suggested by multiple observations made in patients with left-sided PH of various pathogenesis and severity, with acute⁵⁴⁻⁵⁷ and long-term administration⁵⁸⁻⁶¹ of sildenafil. Intriguingly, the benefits of PDE5 inhibitors compared with other classes of pulmonary vasodilators stand on the pulmonary vascular selectivity of PDE5 expression in lung microvessels both in physiological and, even more, pathological conditions, avoiding the untoward systemic hypotensive effect that is typical of other pulmonary vasodilating agents, such as prostanoids and ERAs.⁶

In a PH-HFpEF study by our group,⁴⁰ the hypothesis was tested that chronic PDE5 inhibition (1 year) could specifically target precapillary (mixed) PH and RV function in a selected population of PH-HFpEF associated with right ventricular failure. Forty-four patients were randomized to sildenafil 50 mg TID versus placebo (1:1). PDE5 inhibition with sildenafil was well tolerated and successfully modulated pulmonary vascular tone and right atrial hypertension. In addition, treatment was associated with reduction in RV dilatation, enhanced RV contractile function, and improved measures of alveolar-capillary

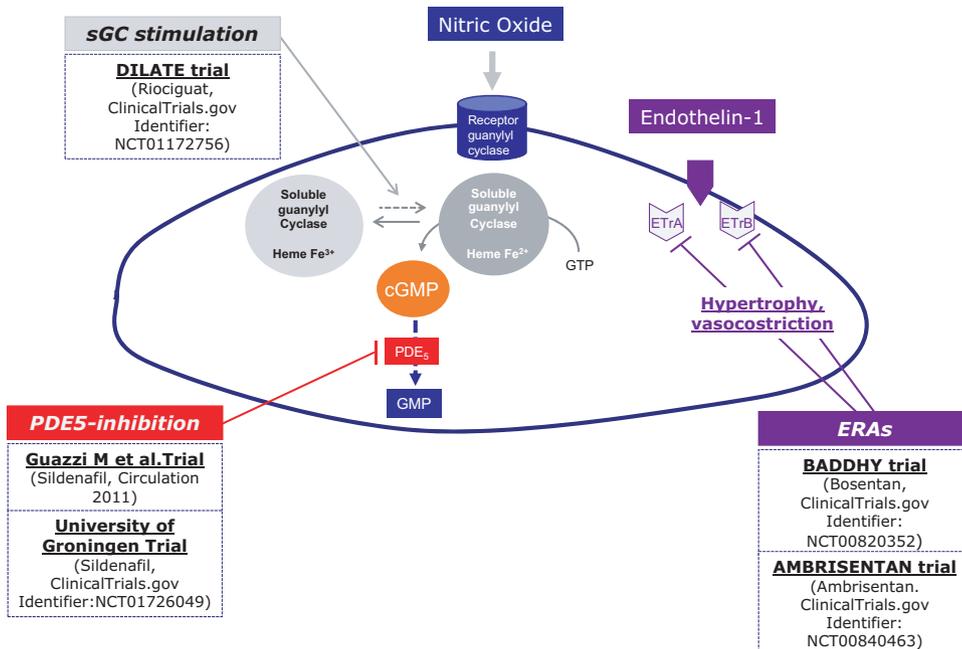


Figure 8. Pathways, pharmacological agents, and relative published and ongoing trials in pulmonary hypertension–heart failure with preserved ejection fraction. cGMP indicates cyclic guanosin-monofosphate; ERAs, endothelin receptor antagonists; ETR_A, endothelin receptor A; ETR_B, endothelin receptor B; GTP, guanosin-trifosphate; PDE₅, phosphodiesterase-5; and sGC, soluble guanylate cyclase.

gas exchange. Less striking, but significant, benefits were observed in the left heart mass, and a 15% reduction in PCWP and improvements in tissue Doppler measures of LV function. Interestingly, the placebo cohort showed a progressive increase in mPAP with time that was related to an increase in PVR rather than PCWP, suggesting a progression of the pulmonary vascular disease rather than LV filling and diastolic function worsening.

The mechanism by which other pulmonary vasodilators increase PCWP whereas PDE5 inhibitors do not, is unclear, but an explanation may be the direct beneficial effects of PDE5 inhibition on LV diastolic stiffness, through cGMP-dependent phosphorylation of titin.⁶²

The multiple effects of sildenafil in our group's study⁴⁰ were consistent with findings in a rat aortic banding model of LV pressure overload leading to HFpEF³⁰ in which PDE5 inhibitors showed beneficial effects on lung endothelial function, pulmonary vascular remodeling, as well as on LVH. Consistently, capillaries and small size arteries showed some degrees of vascular wall thickness that were inversely related to cGMP levels. Even more impressively, the right ventricular chamber showed a reverse geometry and mass reduction with improvement in echo-derived indicators of systolic RV dysfunction, such as TAPSE and pulmonary acceleration time, as observed in humans PH-HFpEF.

There is an additional ongoing single center clinical trial (University of Gronigen; ClinicalTrials.gov Identifier: NCT01726049) that will be replicating the hypotheses of above addressing sildenafil effectiveness in reversing PH in human HFpEF.

In parallel with this evidence, the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial,⁶³ involving larger number of patients with HFpEF, has failed to show any benefit by sildenafil administration 60 mg 3 times a day for 24 weeks. This study, however, was not planned for testing the effects of PDE5 inhibition on pulmonary hemodynamics and right ventricular function. In addition, PH, either of passive or reactive origin, was not a prespecified entry criteria. Thus, the unfavorable results do not preclude that especially patients with significant PH at rest and RV failure may consistently benefit from this promising therapeutic option.⁶⁴

Another class of agents that selectively target the downstream intracellular nitric oxide pathway is the soluble guanylate cyclase (sGC) stimulators. Riociguat is the first of this class of novel therapeutics that has a dual mode of action: it sensitizes sGC to endogenous nitric oxide and directly stimulates sGC independently of nitric oxide.⁶⁵

Riociguat is currently undergoing regulatory review for the indications of PAH and inoperable chronic thromboembolic pulmonary hypertension and is being investigated as a treatment for PH-HFpEF in a Phase 2b study (Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Diastolic Dysfunction, DILATE trial; ClinicalTrials.gov Identifier: NCT01172756) whose primary end point was the mPAP response up to 6 hours after active drug and whose results have been recently presented at the ESC 2013 Congress.⁶⁶ Other than some preliminary data on the hemodynamic effects, the DILATE trial has provided safety and pharmacokinetics information of single different

doses of riociguat in patients with PH-HFpEF. Study findings showed a good safety and tolerability profile with nonsignificant changes in mPAP and PCWP compared with placebo. Riociguat at higher doses (2 mg) improved systemic stroke volume and cardiac index without altering HR, PVR, and TPG.

Figure 8 summarizes pathways, pharmacological agents, and relative ongoing and published trials relative to PH-HFpEF.

Conclusions

In HFpEF, the development of PH, via an increase in left atrial pressure, is the direct consequence of reduced relaxation and enhanced stiffness of the left ventricle, and is now viewed as an important contributor to clinical worsening and increased mortality. This recognition is progressively increasing, making therapeutic interventions aimed at targeting elevated pulmonary pressures as an important challenge for the upcoming years. Out of several classes of pulmonary vasodilators, oral phosphodiesterase-5 inhibitors, because of their strong selectivity for targeting the cGMP pathway in the pulmonary circulation, are increasingly emerging as the most promising ones, in terms of hemodynamic benefits, reverse RV remodeling, and improved functional capacity. GC stimulators show similar properties but have not been extensively tested yet in this subset of patients with PH. Future trials will show whether these pharmacological strategies translate into decreased morbidity and mortality in the growing populations of PH-HFpEF.

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Disclosures

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