

# Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction: Clinical Relevance, Management, and Future Directions

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There are currently 6 million Americans with heart failure, and this number is projected to increase to 8.5 million by 2030. One-half of patients with heart failure have preserved ejection fraction (HFpEF), and the prevalence is increasing. HFpEF can lead to secondary pulmonary hypertension (PH-HFpEF) and is associated with a worsened disease trajectory when present. It is unclear, however, whether PH is a marker of disease severity or a target of treatment in HFpEF. As PH-HFpEF and pulmonary arterial hypertension share several clinical characteristics, the distinction between these 2 syndromes can be difficult. New classification schemes have been proposed to separate those with passive elevations in pulmonary artery pressures from those with more significant pulmonary vascular remodeling. While these classifications have limitations, they are necessary such that pathophysiology, disease trajectory, and pharmacologic therapies can be studied in specific patient subgroups. In this article, we will review the epidemiology of HFpEF, current definitions for both HFpEF and PH in HFpEF, treatment options, and ongoing clinical trials.

## EPIDEMIOLOGY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

The economic cost of heart failure in the United States is estimated to be \$24 billion in 2015, and is expected to double to \$47 billion by 2030.<sup>1</sup> One-half of patients with heart failure have preserved ejection fraction (HFpEF), and in community studies, HFpEF is now the leading cause of heart failure hospitalization.<sup>2,3</sup> Increasing age, obesity, metabolic syndrome, female gender, hypertension, and atrial fibrillation are known to be highly associated with development of this syndrome.<sup>4,5</sup> While historically it has been reported that the prevalence of coronary artery disease (CAD) in HFpEF is lower than heart failure with reduced ejection fraction (HFrEF), recent data suggest that significant CAD can be identified in more than 50% of patients with HFpEF.<sup>6,7</sup>

## PATHOPHYSIOLOGY OF HFPEF

The comorbidities that have been associated with the development of HFpEF have been demonstrated to create a systemic pro-

inflammatory state.<sup>8,9</sup> This inflammation then leads to coronary microvasculature inflammation, impairment of endothelial-cardiomyocyte nitric oxide signaling, and production of fibrosis-inducing cytokines. These pathologic changes contribute to myocyte function and myocardial fibrosis, which cause both increased stiffness and abnormal relaxation during diastole.<sup>10-15</sup> Additionally, left ventricular (LV) *systolic* function is impaired on echocardiographic strain imaging in HFpEF, suggesting that while the calculated LV ejection fraction (LVEF) is normal, the contractility may be impaired.<sup>16,17</sup> Patients with HFpEF can also have chronotropic incompetence, abnormal endothelial function, ischemia, pulmonary hypertension (PH), and right ventricular (RV) dysfunction—all of which can contribute to abnormal fluid handling and exercise intolerance.<sup>18-22</sup> The dominant pathologic finding during exercise can vary from patient to patient.<sup>23</sup>

## DEFINITION AND DIAGNOSIS OF HFPEF

Given the complex pathophysiology and significant heterogeneity within the syn-

drome,<sup>24</sup> HFpEF can be challenging to diagnose. Comorbidities that also cause dyspnea (obesity, chronic kidney disease, chronic obstructive pulmonary disease) are common in this patient group<sup>25</sup> and may delay the recognition of volume overload. Natriuretic peptides may not be elevated, especially in obese patients and subjects who are clinically stable.<sup>26,27</sup> As filling pressures are known to fluctuate between times of decompensation to euvolemia, and even from one day to the next,<sup>28</sup> an echocardiogram or right heart catheterization may not reveal elevated filling pressures unless additional maneuvers are performed. Normal filling pressures, therefore, do not exclude the diagnosis.

Other conditions that mimic HFpEF but are treated differently need to be considered in the initial evaluation, such as valvular heart disease, infiltrative cardiomyopathies, or constrictive pericarditis. The suspicion of an infiltrative process such as amyloidosis, sarcoidosis, and hemochromatosis is increased when there are clues in the history (carpal tunnel for amyloid, diabetes, or arthritis and family history for hemochromatosis, mediastinal lymphadenopathy for sarcoidosis) or when the echocardiogram, electrocardiogram (ECG), or laboratory findings suggest

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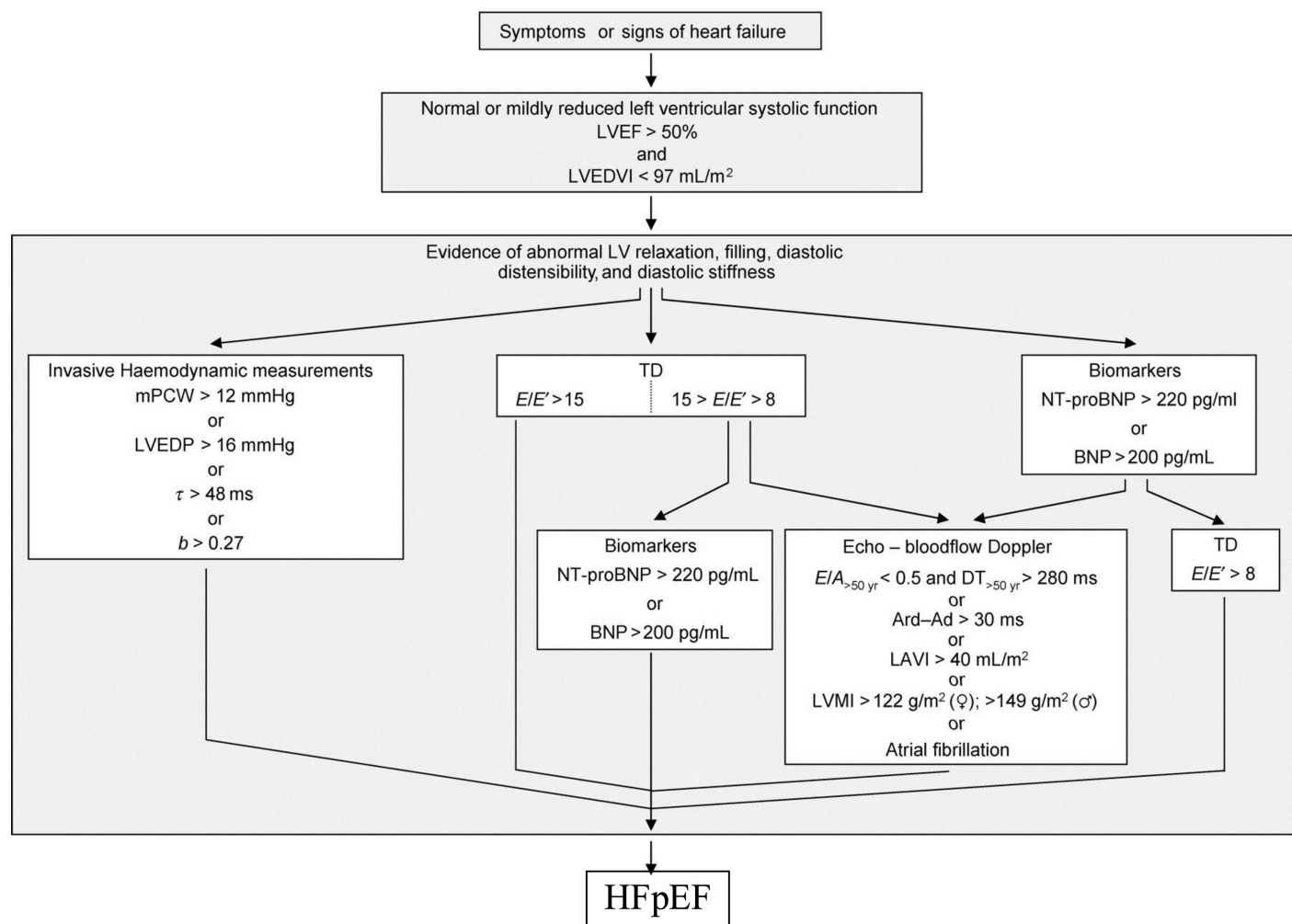


Figure 1: Algorithm for diagnosis of HFpEF. LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic volume index; mPCWP = mean pulmonary capillary wedge pressure; LVEDP = left ventricular end diastolic pressure; BNP = brain natriuretic peptide; DT = deceleration time. Adapted from Paulus WJ, et al. *Eur Heart J*. 2007;28:2539-2550.

these diagnoses. A septal bounce on echocardiogram with normal natriuretic peptides along with a history of chest radiation, recurrent pericarditis, and prior tuberculosis may indicate that further evaluation for pericardial constriction is warranted.

Because of the complexity of the HFpEF diagnosis, algorithms have been proposed to both unify the definition and help clinicians establish the diagnosis. Guidelines from large cardiology societies vary<sup>29</sup>; however, the European Society of Cardiology proposed that the diagnosis of HFpEF can be made by fulfilling the following 3 criteria: 1) signs and symptoms of heart failure, 2) preserved ejection fraction (LVEF  $\geq 50\%$ ), and 3) evidence of diastolic dysfunction either by invasive hemodynamics (left ventricular end diastolic pressure  $> 16$  mm Hg or pulmonary artery wedge

pressure [PAWP]  $> 12$  mm Hg) or by noninvasive myocardial tissue Doppler measures ( $E/E' > 15$ ). If myocardial tissue Doppler is indeterminate ( $15 < E/E' > 8$ ), one of the following additional noninvasive diagnostic modalities can be used to diagnose HFpEF: mitral flow Doppler pattern (E/A ratio and deceleration time), LV mass or left atrial volume index, serum N-terminal pro b-type natriuretic peptide (NT-proBNP) or BNP levels, and/or the presence of atrial fibrillation (Figure 1).<sup>9</sup> Additional tools when the PAWP at the time of right heart catheterization is  $< 12$  mm Hg include saline loading or exercise. While there is no consensus on the exact pulmonary capillary wedge pressure (PCWP) elevation needed for the diagnosis of HFpEF, it has been suggested that an increase in the PAWP to  $\geq 25$  mm Hg with exercise<sup>30</sup>

or  $\geq 15$  mm Hg with a 1 L fluid challenge<sup>31</sup> is consistent with HFpEF.

### PH IN HFpEF

Heart failure with preserved ejection fraction and all conditions that cause left-sided heart failure can also cause secondary PH. The most recent World Health Organization (WHO) classification system categorizes PH due to left heart disease into 4 different categories: PH secondary to HFrEF, PH resulting from HFpEF, PH due to left-sided valve disease, and PH associated with congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies.<sup>32</sup> Among these, PH-HFpEF is the most common.

The true prevalence of PH in patients with HFpEF is unknown as the definitions of both HFpEF and PH in HFpEF continue to evolve. Most of the

prevalence data are based on echocardiographic estimation of the systolic pulmonary artery pressure (PAP) rather than invasive hemodynamic assessment. The reported prevalence of PH-HFpEF among the overall HFpEF population varies widely depending on the group studied and the cutoff value of estimated systolic PAP used to define PH. In a population-based study from Olmsted County, Minnesota, 83% of the patients had estimated systolic PAP  $>35$  mm Hg.<sup>33</sup> In a UK-based study of around 350 HFpEF patients referred to a heart failure clinic, only 18% had an estimated systolic PAP of  $>45$  mm Hg.<sup>34</sup>

Regardless of the underlying left heart pathology, the presence of PH in left heart disease is associated with a worse disease trajectory and overall prognosis. Every 10 mm Hg increase in estimated systolic PAP by echocardiography is associated with a 1.2-fold increased risk of death independent of age.<sup>33</sup> The observed survival in patients with PH-HFpEF may be worse than in those with pulmonary arterial hypertension (PAH) despite having less severe PH and RV dysfunction.

## DIFFERENTIATION OF PH-HFpEF AND PAH

Pulmonary hypertension in HFpEF and PAH share several clinical features including signs and symptoms of heart failure and normal LVEF, making the distinction between these 2 entities difficult. The distinction is important as the safety and efficacy of PAH-specific vasodilator therapies is unclear in patients with PH-HFpEF. These therapies have been shown to be either ineffective or to increase mortality in patients with LV systolic dysfunction.<sup>35,36</sup>

Several clinical, echocardiographic, and hemodynamic characteristics can help differentiate PH-HFpEF from PAH. Compared to PAH, patients with PH-HFpEF are older, more often female, and more frequently have other cardiovascular comorbidities including hypertension, diabetes, obesity, and coronary artery disease.<sup>37</sup> In a multivariate model, simple clinical characteristics without echocardiographic or hemodynamic data were able to differentiate PH-HFpEF from PAH with an area

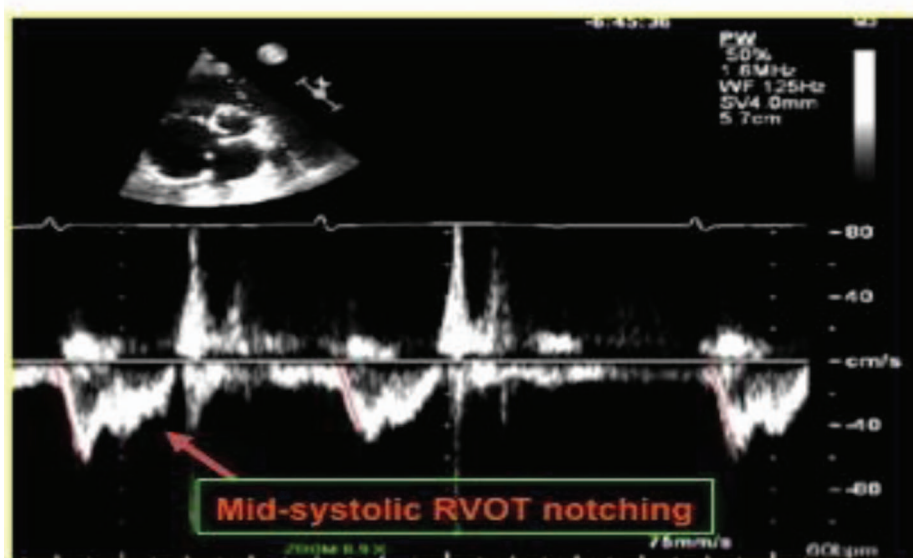
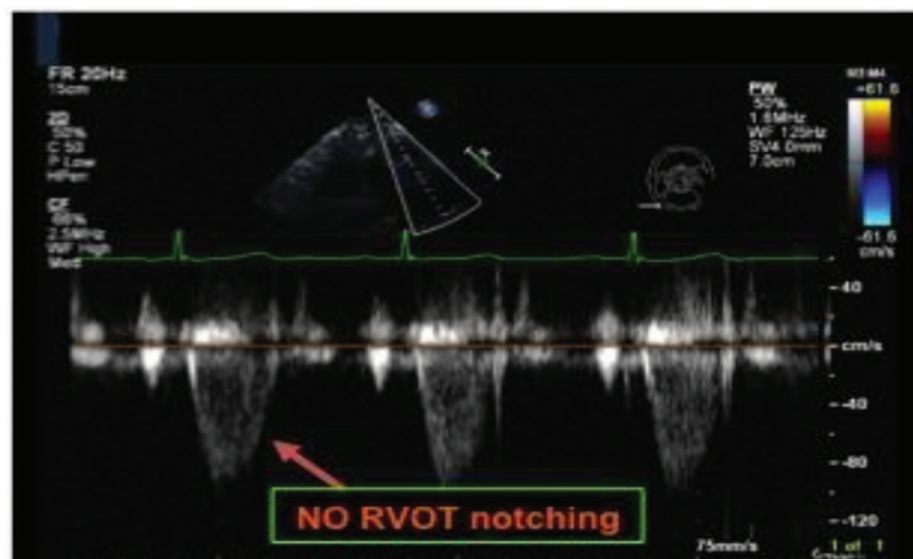


Figure 2: Representative right ventricular outflow tract pulse-wave Doppler tracing with and without notching. RVOT = right ventricular outflow tract.

under the curve of 0.92.<sup>37</sup> On echocardiography, patients with PH-HFpEF often have left atrial enlargement and less frequently have a midsystolic notching pattern on the RV outflow tract Doppler signal (Figure 2).<sup>38</sup> Cardiac MRI derived left atrial volume  $\leq 43$  mL/m<sup>2</sup> can also help to differentiate PH-HFpEF from PAH with an area under the receiver-operating characteristic curve of 0.99.<sup>39</sup>

On hemodynamic evaluation, patients with PH-HFpEF have only a moderate elevation in PAP and pulmonary vascular resistance (PVR).<sup>37</sup> Since the distinction between PAH and PH-HFpEF relies mainly on the accurate measurement of PAWP, meticulous efforts must be made

to obtain an accurate PAWP measurement. The wedge pressure should be measured manually at end expiration<sup>40</sup> instead of relying on the digital wedge pressure, and it should be confirmed with a good wedge pressure wave tracing and by checking an oxygen saturation ( $>94\%$  confirms wedge pressure). Partial balloon inflation should be used when overestimation of wedge pressure is suspected due to partial wedging. If the accuracy of wedge pressure measurement cannot be verified, LV end diastolic pressure should be measured by left heart catheterization.<sup>41,42</sup>

In addition, provocative measures such as saline loading or exercise can help

Table 1. Hemodynamic Variable Abbreviations, Definitions, and Respective Normal Values.

Abbreviation	Long Terminology	Definition	Normal Values
PAM	Mean pulmonary artery pressure	$(\text{PA systolic pressure} + 2[\text{PA diastolic pressure}])/3$	<25 mm Hg
PAWP	Pulmonary artery wedge pressure	A surrogate of left-sided filling pressures	<12 mm Hg*
TPG	Transpulmonary gradient	$\text{PAM} - \text{PAWP}$	<12–15 mm Hg
PVR	Pulmonary vascular resistance	$\text{TPG}/\text{cardiac output}$	<2.5–3 Wood units
DPG	Diastolic pulmonary gradient	$\text{PA diastolic pressure} - \text{PAWP}$	<7 mm Hg

\*A cut point of 12 mm Hg is used for PAWP based on the most current consensus definition of HFpEF by the AHA/ACC.

elicit an abnormal response as patients with the HFpEF syndrome can have a normal resting PAWP or are clinically euvolemic to dry. In a retrospective study of 207 patients, 22% of patients who had PAWP <15 mm Hg at rest were noted to have PAWP >15 mm Hg after 500 cc of acute saline bolus.<sup>31</sup> These patients had very similar clinical, echocardiographic, and hemodynamic characteristics to those with an established diagnosis of PH-HFpEF.

Exercise has also been shown to identify PH-HFpEF in patients with normal resting PAWP. A recent study suggests that exercise may be more sensitive than saline loading for diagnosing PH-HFpEF.<sup>13</sup> A PCWP  $\geq 25$  mm Hg with exercise has been suggested to be consistent with HFpEF.<sup>30</sup>

### CURRENT NOMENCLATURE

Pulmonary hypertension in HFpEF is defined as mean PAP  $\geq 25$  mm Hg in the presence of PAWP >15 mm Hg, signs and symptoms of heart failure, LVEF  $\geq 50\%$ , and absence of significant left-sided valvular heart disease.<sup>41</sup> The cut point of 15 mm Hg for the PAWP in this definition comes from the long-standing definition of WHO Group 2 PH, which splits a normal from an abnormal PAWP at 15 mm Hg.<sup>43</sup> In the European Society of Cardiology algorithm, however, a PAWP of 12 mm Hg or more is needed to diagnose HFpEF. The 12–15 PAWP range remains a gray area but is likely abnormal. With implantable hemodynamic monitoring devices, it is clear that patients who have PAWP <15 mm Hg on one day can change their filling pressures by the next day,<sup>28</sup> suggesting there may be a fair amount of misclassification occurring using our present definitions. Despite these limitations, however, these PH hemodynamic definitions allowed for

the advancement of the PH field and for the dramatic improvement in survival that has been observed. This is also why such effort is currently being put forth to try to further classify PH in left heart disease such that meaningful subgroups with shared pathophysiology can be identified.

The working definitions of PH in left heart disease will be reviewed here. Pulmonary hypertension due to left heart disease including PH-HFpEF is classified into 2 broad categories depending on the presence or absence of intrinsic pulmonary vascular disease, otherwise known as the “precapillary” component. These definitions presently rely on a few key invasive hemodynamics variables defined in Table 1.

### ISOLATED POSTCAPILLARY PH-HFpEF

Isolated postcapillary PH-HFpEF is characterized by passive increase in PAP without significant pulmonary vasoconstriction or remodeling of the small pulmonary arteries. Due to the absence of a precapillary component, the increase in PAP is proportional to the increase in the left-sided filling pressure and therefore normalizes completely with a reduction in the left-sided filling pressure. At this stage, due to the absence of a precapillary component, both the transpulmonary gradient (TPG: the difference between mean PAP and PAWP) and the PVR typically remain within normal limits (TPG <12–15 mm Hg and PVR <2.5–3 Wood units).<sup>44</sup>

### COMBINED POST- AND PRECAPILLARY PH OR “MIXED PH”

Combined post- and precapillary PH-HFpEF is characterized by the presence of precapillary small pulmonary artery remodeling and alveolar wall

thickening in addition to the passive increase in PAP. Chronic elevation in left-sided filling pressure triggers pulmonary arterial vasoconstriction and later intrinsic pulmonary arteriolar remodeling.<sup>45,46</sup> In addition, elevated left-sided filling pressure causes alveolar wall injury, leading to fibrosis and extracellular matrix deposition. This results in alveolar wall thickening, which has also been proposed to contribute to the precapillary component and restrictive lung syndrome with impaired gas exchange.<sup>47</sup> The superimposed precapillary component increases the PAP disproportionate to the left-sided filling pressure and does not normalize with an acute reduction in the left-sided filling pressure. Hemodynamically, combined post- and precapillary PH has been defined as mean PAP  $\geq 25$  mm Hg and PVR  $\geq 2.5$ –3 Wood units (or TPG  $\geq 12$ –15 mm Hg) in the presence of PAWP >15 mm Hg.<sup>44</sup> However, as described below, the entity of combined post- and precapillary PH is currently being redefined based on the diastolic pulmonary gradient (DPG).

### DIASTOLIC PULMONARY PRESSURE GRADIENT

Combined post- and precapillary PH-HFpEF is differentiated from isolated postcapillary PH-HFpEF by the presence of elevated TPG (>12–15 mm Hg) or PVR (>2.5–3 Wood units).<sup>44</sup> However, both TPG and PVR have been demonstrated to be flow-dependent and may not accurately reflect the presence of intrinsic pulmonary arteriolar remodeling.<sup>48</sup> As DPG is not flow-dependent, this has been proposed as a superior measure of the precapillary pulmonary arteriolar remodeling. Hence, at the most recent Fifth World Symposium on PH, new classification and hemodynamic definition for PH due to left heart

disease was proposed based on DPG: isolated postcapillary (mean PAP  $\geq 25$  mm Hg, PAWP  $> 15$  mm Hg, and DPG  $< 7$  mm Hg) and combined postcapillary and precapillary PH (mean PAP  $\geq 25$  mm Hg, PAWP  $> 15$  mm Hg, and DPG  $\geq 7$  mm Hg).<sup>42</sup> Since this nomenclature was put forth, however, the DPG variable has not performed well as a prognostic marker,<sup>49</sup> calling into question the clinical utility and repeatability of DPG in real-world practice.

## LIMITATIONS OF CURRENT DEFINITIONS

Some speculation as to why the DPG may not be as reliable as an indicator as initially hoped for is due to the low absolute number of this measure, which increases its susceptibility to measurement error and its variability with heart rate. Dichotomization at one specific point to split normal from abnormal also leads to loss of information and misclassification. Some of these limitations, however, apply to all hemodynamic definitions. Whether or not hemodynamic classification by DPG will be clinically meaningful remains to be proven. It may be that optimal classification will include hemodynamic variables *after* provocative testing, repeated hemodynamic measures over time, and perhaps clinical variables as well.

The take-home point regarding the current nomenclature is that “mixed PH” is suspected when the PVR, TPG, and/or DPG is elevated beyond what would be expected for passive congestion only and not corrected with acute PAWP reduction in the catheterization lab: these are the patients for whom pulmonary vascular pathology is likely. In addition, a PAWP of  $\geq 12$  is likely abnormal and in the right clinical context is consistent with HFpEF.

## TREATMENT

Presently, the management of PH-HFpEF consists of treating the underlying HFpEF. While guidelines for HFpEF treatment support diuretics and systemic blood pressure control, no specific therapies have been demonstrated to decrease mortality or reduce heart failure

hospitalizations in a large randomized clinical trial.<sup>50</sup> Spironolactone was recently shown to decrease hospitalization in patients with HFpEF; however, there was no effect on mortality.<sup>25</sup> Revascularization in patients with HFpEF and concomitant significant CAD was associated with preservation of ejection fraction and a reduction in mortality in one retrospective single-center study.<sup>6</sup> While this was not a randomized clinical trial, it underscores the importance of evaluating for ischemia if within the goals of care.

## ROLE OF PULMONARY VASODILATOR THERAPIES IN PH-HFpEF

Pulmonary arterial vasodilator therapies improve functional capacity, time to clinical worsening, and survival in patients with PAH. The efficacy of PAH-specific therapies in PH-HFpEF is unclear, and there is a theoretical concern that these therapies may cause worsening pulmonary edema by increasing pulmonary blood flow in the presence of elevated left-sided filling pressures.<sup>35,51-53</sup> Endothelin receptor antagonists and parenteral prostacyclin (intravenous epoprostenol) therapy have been shown to be either neutral or increase mortality in patients with LV systolic dysfunction.<sup>35,52</sup> Only a limited number of clinical trials have thus far evaluated the safety and efficacy of pulmonary arterial vasodilator therapies in PH-HFpEF. These trials are either neutral or small single-center studies; therefore, PAH-specific therapies are currently not approved for the treatment of PH-HFpEF.

### *Phosphodiesterase Type 5 Inhibitors*

Of all the various PAH-specific therapies, phosphodiesterase type 5 (PDE5) inhibitors have been studied the most in PH-HFpEF. In a single-center randomized clinical trial, 44 patients were randomized to either placebo or sildenafil 50 mg 3 times per day for 12 months.<sup>54</sup> Cardiac hypertrophy and elevated DPG ( $\sim 9$  mm Hg) were required for trial entry, consistent with combined post- and precapillary PH in the setting of HFpEF. After 6 months, there were significant improvements in

RV function as demonstrated by decreased right atrial pressure ( $10.6 \pm 3.6$  mm Hg vs  $22.0 \pm 5.2$  mm Hg), increased tricuspid annular plane systolic excursion ( $19.2 \pm 2.3$  mm vs  $10.6 \pm 2.3$  mm), and increased RV mean systolic ejection rate ( $276 \pm 25.1$  mL/s vs  $231 \pm 24.2$  mL/s) in the sildenafil-treated group compared to placebo. There were also significant changes in the pulmonary vasculature as mean PAP ( $22.3 \pm 3.7$  mm Hg vs  $37.8 \pm 4.9$  mm Hg) and PVR ( $1.18 \pm 0.50$  Wood units vs  $3.42 \pm 1.02$  Wood units) decreased significantly with sildenafil therapy compared to placebo at 6 months. The beneficial effects of sildenafil persisted at 12 months and sildenafil was associated with improvement in quality of life. Collectively, these data suggest sildenafil may be a useful treatment in PH-HFpEF patients. However, this study did not include hospitalization for heart failure or mortality given its small size. It is unclear whether these hemodynamic and echocardiographic improvements will translate to a meaningful clinical improvement.

In contrast, the positive effects of sildenafil were not observed in the RELAX study, a multicenter clinical trial that assessed sildenafil in HFpEF patients.<sup>55</sup> Pulmonary hypertension was not required for trial entry and the trial did not specifically investigate pulmonary hemodynamics and RV function. Another trial assessing sildenafil in PH-HFpEF has recently been completed in Germany (NCT01726049) and the results are pending. This trial will determine how 12 weeks of treatment with sildenafil affects invasive hemodynamics and peak  $\text{VO}_2$ .

### *Soluble Guanylate Cyclase Stimulators*

The DILATE-1 trial assessed riociguat, a soluble guanylate cyclase activator, in the PH-HFpEF population.<sup>56</sup> DILATE-1 compared varying doses of riociguat: 0.5 mg in 8 patients, 1 mg in 7 patients, and 2 mg in 10 patients compared to placebo (in 11 patients) to determine the short-term effects on invasive hemodynamics 6 hours after administration of the study drug. There was no difference in the change in mean PAP between baseline and 6-hour time

points in the riociguat 2 mg (n=10) vs placebo (n=11) groups. Vericiguat, another soluble guanylate cyclase stimulator, is currently being evaluated for HFpEF in SOCRATES-HFpEF, a 12-week, double-blind, randomized, parallel-group, placebo-controlled, Phase 2 clinical trial (clinicaltrials.gov: NCT01951638).

### Endothelin Receptor Antagonists

In a randomized placebo-controlled trial of 192 patients, 6 months of sitaxsentan, a selective endothelin A receptor antagonist, treatment improved treadmill exercise time compared to placebo (90 seconds vs 30 seconds).<sup>57</sup> However, there was no change in LV mass or trans-mitral diastolic parameters. The presence of PH was not a prerequisite for inclusion in this trial, and the effect of sitaxsentan on pulmonary hemodynamics was not assessed. The BADDHY trial is assessing the impact of 12 weeks of bosentan treatment on 6-minute walk test, hemodynamics via echocardiography, and symptomatic burden (NCT00820352).

### CONCLUSION

In summary, the incidence of HFpEF is increasing rapidly. The diagnosis can be difficult to make and the definition of the HFpEF syndrome is still evolving. Pulmonary hypertension secondary to HFpEF is very common and associated with a worsened disease trajectory when present. Treatments targeting not only HFpEF but also PH associated with HFpEF are urgently needed. The classification scheme describing the various hemodynamic profiles of PH related to left heart disease has limitations, but has recently evolved to try to help categorize patients in meaningful ways. Several novel treatments for PH-HFpEF and HFpEF are currently being tested, giving hope to the prospect of new treatments for these challenging syndromes in the near future.

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