Left Ventricular Dysfunction With Pulmonary Hypertension  
Part 1: Epidemiology, Pathophysiology, and Definitions

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The worsening heart failure (HF) epidemic and the associated healthcare costs pose a major burden to public health and the healthcare system.1 Despite significant therapeutic advances, outcomes for patients with HF remain suboptimal.2–4 Importantly, most clinical trials with novel agents in HF during the past decade have yielded neutral or modest results.5 The reasons for these unfavorable trends are complex.6 One issue gaining wide acceptance is that the one-size-fits-all approach to HF therapies is unlikely to be beneficial, especially when new therapies are given on top of comprehensive neurohormonal blockade. Thus, it is crucial for the development of novel therapies to better understand the various HF phenotypes and their pathophysiology and subsequently target relevant pathways in such subgroups of patients.

Pulmonary hypertension (PH) is a heterogeneous entity with different causes leading to increased pressures in the pulmonary circulation. PH is a major and frequent consequence of left-sided HF, irrespective of left ventricular ejection fraction (LVEF) or presence of valvular disease.7–9 The presence of PH is associated with worse HF outcomes, regardless of LVEF and stage of HF,7,8 and prognosis is further aggravated when right ventricular (RV) dysfunction ensues, posing a number of diagnostic and therapeutic dilemmas that influence decision making.10,11 A combination of elevated LV filling pressures, reactive pulmonary arterial vasoconstriction, and pulmonary vascular remodeling results in PH secondary to left heart disease.12 Abnormal hemodynamic parameters indicative of PH in HF patients receiving optimal therapy may represent a potential therapeutic target.

In this 2-part review, we summarize the current opinions and evidence related to PH in HF. In the first part, we describe the definitions and classification, cause, and epidemiology of PH in HF. In the second part, we discuss its prognostic impact, the contemporary evaluation approaches, the challenges and results of the clinical trial targeting PH in HF, and potential ways to overcome these challenges in future.

Classification of PH

The definition of PH has evolved during the past decades. The widely accepted upper level of normal mean pulmonary artery pressure (mPAP) is ≥25 mm Hg at rest obtained invasively and covers all the 5 main PH groups defined by the Dana Point convention (Table 1).14–16 Pulmonary capillary wedge pressure (PCWP) is an important variable for characterizing PH, and various hemodynamic types of PH can be identified based on PCWP, pulmonary vascular resistance (PVR), and cardiac output.

The distinction between precapillary (normal PCWP ≤15 mm Hg) and postcapillary (elevated PCWP >15 mm Hg) PH is extremely important from a therapeutic perspective. Indeed, therapies effective in the precapillary PH may be detrimental in the postcapillary PH, or vice versa.18,19 Precapillary PH includes Groups 1, 3, 4, and 5, whereas postcapillary PH refers to Group 2 (Table 1) PH due to left-sided heart disease.20 The latter is characterized by the combination of elevated mPAP (≥25 mm Hg) and elevated PCWP (>15 mm Hg).

Types of PH in HF

Within Group 2 PH, there are subtypes characterized by the presence or absence of pulmonary vascular disease, which may coexist with elevated PCWP (Figure 1). The transpulmonary pressure gradient (TPG), defined as mPAP minus PCWP, and the PVR, calculated as TPG divided by the cardiac output, can help differentiate among the subtypes of Group 2 PH.13–15 The normal TPG is 6±2 mm Hg,22 but for clinical purposes, a gradient of <12 to 15 mm Hg is considered acceptable. Similarly, PVR is normally 0.9±0.4 Wood Units (WU),23 but values <2.5 to 3.0 WU are used in practice to differentiate the Group 2 PH subtypes.13–15

Passive PH

Group 2 PH is considered passive when the pressure downstream of pulmonary arteries is the dominant cause of elevated mPAP (Figure 1). By convention, this occurs when the TPG and the PVR are normal. This type of PH is seen most often in the early stages of HF and represents the form with the highest prevalence. The absence of elevated TPG (and PVR) implies that there are no significant abnormalities in the pulmonary artery structure or function. In this case, PH is caused by high left heart pressures and may remit with HF-specific interventions such as diuresis and systemic

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out-of-proportion is used when mPAP is severely elevated in PVR to pharmacological interventions. Additionally, the term fixed or irreversible, depending on the response of TPG and PVR to pharmacological interventions may lead to labeling PH as fixed, emerging data have reported delayed reversibility after heart transplantation or LV assist device implantation. The potential for delayed reversibility might be considered when candidacy for heart transplantation is evaluated. Although acute reversibility is an important selection criterion for heart transplantation, longer term interventions to reduce PVR could be considered when an acute vasodilator challenge is unsuccessful. Often PVR will decline after 24 to 48 hours of treatment consisting of diuretics, phosphodiesterase 3 inhibitors, and vasoactive agents, although some patients may require therapy for weeks before an acceptable reduction in PVR is obtained. These observations may have implications for long-term pharmacological treatments.

Reactive or Mixed PH

When the TPG and PVR are elevated, Group 2 PH is referred to as reactive (or active) or mixed, indicating that high mPAP is a combination of elevated PCWP in conjunction with functional/structural abnormalities of the pulmonary vasculature. Reactive PH is in turn further classified into reversible and fixed or irreversible, depending on the response of TPG and PVR to pharmacological interventions. Additionally, the term out-of-proportion is used when mPAP is severely elevated in concert with only modestly elevated left-sided pressures. The degree of PCWP elevation, or its chronicity, that qualifies as out-of-proportion remains unresolved and is debated. Unlike passive PH, reactive Group 2 PH is considered a plausible target for therapy with a pulmonary arterial specific agent. Intervention that solely lowers the PCWP would not be expected to normalize the TPG and PVR in mixed PH in the short term. However, pulmonary vasodilator therapy may reverse the active component and lower TPG and PVR to clinically acceptable levels in a proportion of patients with the reversible form of reactive PH. It is presumed that at this stage there are functional, but not significant structural, abnormalities of the pulmonary vascular bed. The reversibility of TPG and PVR in mixed PH is an important selection criterion for heart transplantation candidacy and a prognostic indicator of posttransplant outcomes.

If PVR cannot be reduced to <2.5 to 3 WU, PH is considered fixed. At this stage, both functional and structural abnormalities of the pulmonary vascular bed are presumed to exist, and histological changes may be indistinguishable from precapillary PH. Pathological findings in the pulmonary vasculature have both similarities and differences among the various PH groups. The histological findings in the pulmonary vasculature of patients with severe Group 1 PH are a combination of small pulmonary arterial medial and adventitial thickening, occlusive neointima proliferation, and complex plexiform lesions. Group 2 PH is characterized by enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, and lymphatic vessel and lymph node enlargement. Distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis as a result of remodeling mediated by smooth muscle cells, with eccentric intima lesions and medial thickening. The extent and pattern of arterial remodeling is similar to that seen in Group 1 PH. In a study investigating the structural changes in the pulmonary vasculature in patients who died after heart transplant, the main pathological finding was medial hypertrophy of muscular pulmonary arteries. This increase in medial thickness was greater than that observed in patients with idiopathic PH despite a comparable elevation of pulmonary pressures. In this specific population, intimal fibrosis of pulmonary arteries was not observed; however, the majority of cases had mild PH. Intimal fibrosis is common in the pulmonary vasculature. All these structural changes affect response to vasodilators (fixed PH). However, it is important to note that although lack of reversibility with acute pharmacological interventions may lead to labeling PH as fixed, emerging data have reported delayed reversibility after heart transplantation or LV assist device implantation. The potential for delayed reversibility might be considered when candidacy for heart transplantation is evaluated. Although acute reversibility is an important selection criterion for heart transplantation, longer term interventions to reduce PVR could be considered when an acute vasodilator challenge is unsuccessful. Often PVR will decline after 24 to 48 hours of treatment consisting of diuretics, phosphodiesterase 3 inhibitors, and vasoactive agents, although some patients may require therapy for weeks before an acceptable reduction in PVR is obtained. These observations may have implications for long-term pharmacological interventions.

### Table 1. Current Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Group 1: Pulmonary arterial hypertension (PAH)</th>
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<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
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<tr>
<td>1.2 Heritable</td>
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<tr>
<td>1.2.1. BMPR2</td>
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<tr>
<td>1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)</td>
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<tr>
<td>1.2.3 Unknown</td>
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<tr>
<td>1.3 Drugs and toxins induced</td>
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<td>1.4 Associated with</td>
</tr>
<tr>
<td>1.4.1 Connective tissue diseases</td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart diseases</td>
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<tr>
<td>1.4.5 Schistosomiasis</td>
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<td>1.4.6 Chronic hemolytic anemia</td>
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<td>1.5 Persistent pulmonary hypertension of the newborn</td>
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<tr>
<th>Group 2: Pulmonary hypertension due to left heart disease</th>
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<tbody>
<tr>
<td>2.1 Systolic dysfunction</td>
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<tr>
<td>2.2 Diastolic dysfunction</td>
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<tr>
<td>2.3 Valvular disease</td>
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<tr>
<th>Group 3: Pulmonary hypertension because of lung diseases and hypoxia</th>
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</thead>
<tbody>
<tr>
<td>3.1 Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>3.2 Interstitial lung disease</td>
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<tr>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
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<tr>
<td>3.4 Sleep-disordered breathing</td>
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<td>3.5 Alveolar hypventilation disorders</td>
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<td>3.6 Chronic exposure to high altitude</td>
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<td>3.7 Developmental abnormalities</td>
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<tr>
<th>Group 4: Chronic thromboembolic pulmonary hypertension</th>
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<th>Group 5: PH with unclear and multifactorial mechanisms</th>
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<tbody>
<tr>
<td>5.1 Hematologic disorders: myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangiioleiomysomatosis, neurofibromatosis, vasculitis</td>
</tr>
<tr>
<td>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td>5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</td>
</tr>
</tbody>
</table>

vasodilators. Passive PH would generally not be considered a plausible target for therapy with a pulmonary arterial selective agent.

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therapies as well. Studies using the phosphodiesterase 5 inhibitors in patients with advanced, pretransplant HF, and severe PH have shown beneficial effects on hemodynamics and clinical status, whereas sildenafil seems to improve post-transplant survival.32,33

PCWP Versus LV End-diastolic Pressure
To complicate things further, data suggest that PCWP does not always correlate closely with LV end-diastolic pressure (LVEDP). A retrospective study of patients undergoing left and right heart catheterizations (RHCs) reported that ≥50% of patients with PCWP <15 mm Hg had elevated LVEDP to >15 mm Hg.34 This has led some to suggest that left heart catheterization be broadly applied in the evaluation of PH. However, measuring PCWP at mid-A wave after careful verification by characteristic atrial waveforms and oximetry confirmation (saturation >93%) of appropriate right heart catheter placement shows better correlation with LVEDP. Physiologically, it can be argued that an appropriately measured PCWP is more important when evaluating the cause of PH than LVEDP, because this is the immediate downstream pressure that adds in series with the product of flow (cardiac output) and resistance (PVR). If an adequate quality PCWP tracing cannot be obtained, direct measurement of LVEDP is indicated in the evaluation of PH.

Challenges in the Classification of PH Related to HF
Careful phenotyping of PH secondary to HF is important for characterization of drug responses and selection of patients for clinical trials, especially mechanistic studies. In the case of mixed PH, especially in a setting of older patients with normal EF, it might be challenging to distinguish between PH due to HF (Group 2), PH of pulmonary disease origin (Group 3), and pulmonary arterial hypertension (Group 1). Thus, in cases of mixed PH, ruling out causes unrelated to LV dysfunction is critical. Among studies investigating Group 2 PH, this has not been done uniformly.35–38 Not surprisingly, the results of these studies are conflicting, with reactive PH predicting mortality only in one study.38

Pathophysiology of PH in HF
The pathophysiology of Group 2 PH is complex (Figure 2). Patients with left heart disease may develop both passive and reactive PH, with all cases having a passive component associated with increased left atrial pressure. In patients with HF with reduced EF (HFREF), both diastolic dysfunction and mitral regurgitation may lead to an increase in left atrial pressure, whereas in patients with HFP EF, diastolic dysfunction is the main cause of increased pressures because of the increased passive stiffness. Thus, increased LV filling pressures, irrespective of LVEF, lead to pulmonary venous hypertension and postcapillary PH. The hydrostatic pressure in turn creates a mechanical injury to the alveolar-capillary barrier that fractures the delicate structure of the capillary wall, known as alveolar-capillary stress failure (acute phase).41 When the elevation in venous pressures is chronic, excessive, and persistent, it triggers a multistep adaptive process that involves the microcirculation and the alveolar wall and leads to excessive production and accumulation of collagen IV in the extracellular matrix.42,43 Collagen accumulation causes functional and structural changes in the pulmonary vasculature, initially in the capillaries and later on in the arterioles and arteries (chronic phase).7 The role of endothelium is important in this process. Endothelial dysfunction secondary to injury plays a
Figure 2. Pathophysiology of Group 2 pulmonary hypertension. Left heart disease causes elevation of left atrial pressure, which in turn leads to increased hydrostatic pressure in pulmonary capillaries. Diastolic dysfunction is the main contributor of increased atrial pressure in heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and valvular heart disease. Mitral regurgitation and left ventricular (LV) hypertrophy contribute further to increased atrial pressure in HFrEF and valvular heart disease, respectively. Elevated hydrostatic pressure causes injury to the alveolar-capillary barrier in the acute phase, whereas chronically elevated pressure triggers various pathways involving the microcirculation and the alveolar wall. Mechanical injury because of hydrostatic pressure (alveolar-capillary stress failure) leads to disruption of the alveolar-capillary membrane, resulting in transition from interstitial leakage of protein (low permeability stage) to alveolar lumen leakage of protein and erythrocytes (high permeability stage). High permeability pulmonary edema activates matrix metalloproteinases (MMPs), causing degradation of matrix proteoglycan and alteration in the composition of membrane units, which in turn causes increased endothelial membrane fluidity. Initially, alveolar-capillary stress failure is a reversible phenomenon. However, chronic pressure elevation leads to remodeling and thickening (excessive collagen deposition) of the alveolar-capillary membrane, a process perpetuated by locally produced hormones (eg, angiotensin II [Ang II] and inflammatory markers (eg, tumor necrosis factor-α [TNF-α]). The increased capillary pressure also promotes hypertrophy and fibrotic changes in the pulmonary arteries and veins with medial hypertrophy of smooth muscle cells (SMCs) and finally disruption of the elastic lamina. Imbalance in endothelin-1 (ET-1) and nitric oxide (NO) release and genetic factors influence these pulmonary vascular structural changes. EC indicates endothelial cell.
The endothelium-mediated local control of vascular tone is pressure through the kidney. The latter impairs renal sodium venous pressure with a consequent reduction in the filtration to release of atrial natriuretic peptides, and increases renal interstitial fluid accumulation, which in turn can further increase pulmonary vasculature resistance occurs, because of the interlinked dynamics, individual genetic characteristics may affect development of PH.47

**Right Ventricle in PH**

PH affects RV function also. Chronic exposure of RV to elevated afterload, and often to elevated preload as a result of RV dilation and functional tricuspid regurgitation, leads to RV systolic dysfunction. The prognosis of patients with PH is further aggravated by RV dysfunction.10,11 The development of RV dysfunction portends worsening of HF symptoms. Compromised RV output facilitates edema formation by raising right atrial pressure. In addition, a vicious circle of increased pulmonary vasculature resistance occurs, because of the interstitial fluid accumulation, which in turn can further increase resistance. RV dysfunction causes atrial distention, leading to release of atrial natriuretic peptides, and increases renal venous pressure with a consequent reduction in the filtration pressure through the kidney. The latter impairs renal sodium excretion and can trigger positive feedback loops that lead to refractory HF.48

**Echocardiographic Definition of PH**

The gold standard for the evaluation of pulmonary hemodynamics is RHC.49 However, RHC is an invasive procedure with associated risks, complications, cost, and need for an experienced operator and team to both perform the procedure and obtain reliable results. Therefore, RHC is not suitable as a screening tool for all patients with suspected PH, especially on a broad basis, for example, those individuals with Stage C HF. Accurate noninvasive alternatives to assess pulmonary hemodynamics are, therefore, desirable. Echocardiography is a suitable screening tool, and also provides valuable information on cardiac structure and performance, important for identification of the cause of PH. RV systolic pressure (RVSP) by Doppler echocardiography can provide an estimate of the systolic PAP (sPAP) with acceptable accuracy in patients with HF,50,51 especially in those with advanced disease.52,53 Variable criteria have been used for echocardiographic definition of PH.54 However, an RVSP ≤36 mm Hg makes PH very unlikely,54,55 whereas values ≥45 mm Hg have been consistently associated with worse prognosis in various HF populations.50,56–58 Using the tricuspid regurgitant velocity, a <2.5 m/s may be classified as normal, 2.5 to 2.8 m/s as borderline, and >2.8 m/s as indicative of PH.59 Concomitant evaluation of other echocardiographic parameters is also recommended, which we will discuss in the second part of this review.

**PH in Valvular Heart Disease**

The structural alterations present in valvular heart disease result in hemodynamic abnormalities that in turn lead to PH, the prevalence of which increases in parallel with the severity of the defect and the associated symptoms. Mitral valve disease results in elevated left atrial pressure, which in turn leads to PH accompanied by structural alterations of the pulmonary vasculature, especially when mitral stenosis is present. Increased levels of endothelin-1 have been observed in patients with severe mitral stenosis.60 Mitral valve disease has been the prototype of cardiac disease associated with PH,61,62 and the presence of PH in mitral valve disease plays a key role in the management of the primary disease.63,64 Mitral stenosis, when moderate to severe, is associated with PH in the majority of patients, although the degree of PH is variable. In candidates for mitral valvuloplasty, the prevalence of PH has been reported to be as high as 75%.65 In patients with chronic isolated mitral regurgitation and preserved LV function, the prevalence of PH defined as sPAP ≥30 mm Hg by RHC was 76%,66 whereas sPAP ≥50 mm Hg was present in 17% of patients.66 In patients with asymptomatic mitral regurgitation, exercise-induced PH defined as sPAP >60 mm Hg during exercise was very common, with a reported prevalence of 46%, whereas resting PH defined as sPAP >50 mm Hg in the same population was only 15%.67 These findings were confirmed by an independent study showing that almost 50% of patients with asymptomatic mitral regurgitation have exercise-induced PH.68

Aortic stenosis results in PH by inducing LV hypertrophy and reduced LV diastolic function, which in turn leads to elevated pulmonary pressures. Over time, structural changes in the pulmonary vasculature occur. In patients with severe aortic stenosis, the prevalence for PH has been reported to reach 50%, defined as sPAP >30 mm Hg,69 whereas 29% of patients with severe aortic stenosis had PH when PH was defined as sPAP >50 mm Hg.70 Mild-to-moderate and severe PH was present in 50% and 15% of patients, respectively, in another study.71 Albeit less frequently, aortic regurgitation can also lead to PH secondary to chronic elevation of LVEDP, which in turn leads to an increase in left atrial and pulmonary artery pressures. The prevalence of PH in severe aortic regurgitation has been reported to be 10% to 20%.72

**Epidemiology of PH in HF**

**Determinants of PH**

The severity of PH in left heart disease is thought to be a function of the cumulative exposure to pulmonary venous hypertension over time, regardless of LV systolic function or HF stage.73,74 Consequently, LV filling pressures and degree of mitral regurgitation play a major role in the development and progression of PH.75 Chronic elevation of LV filling pressures is reflected in left atrial enlargement, which strongly correlates with sPAP in patients with HF and reduced or preserved LVEF.76 The severity of PH parallels that of mitral regurgitation in patients with advanced HF.77 Genetic predisposition
may also play a role in the development of PH in patients with HF and LV systolic dysfunction. Data on factors predisposing to reactive PH are conflicting. Berger et al identified no clinical, echocardiographic, or laboratory parameters predictive of reactive PH (compared with passive PH), whereas recently a study in Japanese patients reported that women are more prone to reactive PH.

Increased PAP directly affects RV systolic function, and the severity of RV systolic dysfunction strongly parallels progression of LV failure in patients with severe systolic HF. Diastolic dysfunction and severe tricuspid regurgitation further aggravate RV dysfunction. Finally, reduced RV systolic function is more frequently encountered among patients with nonischemic cause of LV systolic dysfunction, independent of PH and LV status.

The Role of Diastolic Dysfunction

The importance of diastolic dysfunction in the development of PH in patients with HFrEF is increasingly being recognized. In patients with HFrEF, the severity of concomitant diastolic dysfunction rather than LVEF or cardiac output correlates best with the severity of PH in one study. Recently, a study investigating the role of LV diastolic properties in patients with HFrEF elucidated the significant contribution of LV diastolic dysfunction to PH. The probability of PH was a function of diastolic dysfunction indices (higher E/e' and shorter deceleration time) and mitral regurgitation; of note, LVEF was not a predictor of PH in this study. An E/e' ≥15 and deceleration time ≤150 ms, reflecting at least moderate LV diastolic dysfunction, were highly predictive of RVSP ≥45 mm Hg.

Diastolic dysfunction associated with valvular disease, reduced LVEF, or in isolation, is the common mediator of chronic pulmonary venous hypertension and secondary PH. Older persons would be more vulnerable to development of PH, considering that age-related vascular stiffening, including the pulmonary vasculature, has been consistently reported. Moreover, age-related increases in arterial stiffening are worse in women than in men, indicating that older female patients who develop HF with diastolic dysfunction may also be more prone to PH. The prevalence of LV diastolic dysfunction in the general population varies from 11.1% to 34.7% depending on of the population studied, the criteria applied, and the imaging modality used. Similar to LV diastolic dysfunction prevalence, the normal PAP also increases with age, pointing to a common vascular aging process.

PH in HFrEF

The reported prevalence of PH in patients with HFrEF varies depending on the patient population studied, the chronicity of the disease, and the definition used (Table 2). The presence and severity of PH within an individual patient may vary not only longitudinally over time, but also in the short term depending on their compensation status. In a recent study from the United Kingdom, among 413 patients with newly diagnosed HF and measured RVSP, 25% had a tricuspid gradient >35 mm Hg, corresponding to an RVSP >45 mm Hg. However, these patients represented only 30% of the entire cohort, because RVSP was not obtained in the remaining participants. In the same study, a tricuspid gradient >35 mm Hg was present in 29% of those with HFrEF. In a study using peak velocity of tricuspid regurgitation to assess sPAP in patients with severely reduced LVEF, the prevalence of tricuspid regurgitation jet velocity >2.5 m/s was 25.9%. In a large retrospective cohort from Scotland, among patients with reduced LVEF, loop diuretics prescription, and measured RVSP, 47.5% had RVSP >45 mm Hg. Prevalence increases with progression of HF. In 377 consecutive New York Heart Association (NYHA) Class II to III outpatients with LVEF <35%, PH by RHC was present in 62.3% of patients; however, the definition of PH used in this study was mPAP >20 mm Hg, underscoring the impact of population selection and definition on prevalence of PH. Overall, the prevalence of PH in HFrEF seems to range from 25% to >50%.

PH in Advanced HF

In advanced HF, the measure used to define PH (PAP versus PVR) affects prevalence estimates. In 320 patients with severe LV systolic dysfunction (LVEF 23±9%), PVR was normal (<1.5 WU) in 28%, mildly elevated (1.5–2.49 WU) in 36%, moderately elevated (2.5–3.49 WU) in 17%, and severely elevated (>3.5 WU) in 19% of the patients; 35% to 40% of patients in NYHA class III and IV had moderately or severely elevated PVR (>2.5 WU). Similarly, PH defined as PVR ≥2.5 WU was present in 41.3% of a pretransplant HF population a median of 2.7 months before transplantation. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, PH was present in 47% of hospitalized HF patients with LVEF ≤30%, using a definition of mPAP ≥25 mm Hg at rest, PCWP >15 mm Hg, and PVR ≥3 WU. These data are in line with an earlier observational study on transplant recipients where PVR >2.5 was present in 50.4% of the transplant recipients. Thus, in advanced HF populations, the prevalence of PH requiring evaluation for reactive PH (PVR ≥2.5) is 40% to 50%.

PH in HFpEF

Similarly, the prevalence of PH in HFpEF depends on the population studied and the definition used for PH, and also, on the criteria used for HFpEF diagnosis. In the UK study, a tricuspid gradient >35 mm Hg was present in 18% of 143 patients with HFpEF and measured RVSP. In contrast, among 244 patients with HFpEF from Olmsted County, Minnesota, 83% had PH by echocardiography using a definition of RVSP >35 mm Hg. However, the cutoff used to define PH in this study was low, especially considering that normal RVSP increases with age and a mixed population of outpatients and inpatients with HF was studied. The median RVSP in that study was 48 mm Hg, implying that PH prevalence with a definition of >45 mm Hg would have been closer to 50%. In all, the prevalence of PH in HFpEF varies widely, from 18% to >50%, and data from prospective epidemiological studies are limited.

Exercise-induced PH

Although most data on PH pathophysiology are based on resting hemodynamics, patients develop symptoms indicative of PH more often during exercise. PAP response to exercise has been used as a diagnostic criterion for PH, and exercise
remains a significant physiological stressor for patients with PH.\(^{15}\) However, its role in the evaluation of PH has been questioned, mainly because of the age-dependent increase of mPAP during exercise,\(^{10}\) limited normative data in various postures during exercise,\(^{54}\) and different types and protocols of exercise tests.\(^{54}\) Exercise-induced PH is common in HF\(^{35,36,96,102}\) and is a prognostic factor, especially when accompanied by increased LV filling pressures during exercise.\(^{103}\) The response of PAP to increases in cardiac output during exercise provides valuable insights into the pathophysiology of exercise intolerance and cardiovascular reserve.\(^{104}\) In a study on patients with exertional dyspnea and preserved (≥50%) LVEF referred for invasive exercise testing, more than half were diagnosed with HFpEF; 88% developed mPAP >30 mm Hg during exercise.\(^{35}\) However, this was a highly selected cohort with normal resting hemodynamics and cardiac load biomarkers despite exertional symptoms, and the European Society of Cardiology criteria\(^{105}\) would have identified one third of cases as HFpEF patients before testing.\(^{35}\) Also, the definition of HFpEF was itself based on hemodynamics.\(^{35}\) Another study reported that almost half the patients referred for invasive exercise evaluation had exercise-induced PH because of pulmonary venous hypertension.\(^{36}\) The authors suggested that exercise-induced PH may be part of the continuum from normal to severe pulmonary vascular disease.\(^{36}\) In this study, however, most patients were referred because of exercise intolerance, making it unclear whether

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Method</th>
<th>Definition</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
<td>Abramson 1992(^a)</td>
<td>108</td>
<td>Dilated cardiomyopathy; mean LVEF 17.2%</td>
<td>Echo</td>
<td>TR jet velocity &gt;2.5 m/s</td>
<td>25.9%</td>
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<tr>
<td>Butler 1999(^a)</td>
<td>320</td>
<td>Ambulatory patients for Tx evaluation; LVEF 23±9%</td>
<td>RHC</td>
<td>PVR &gt;1.5 WU</td>
<td>72%</td>
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<tr>
<td>Ghio 2001(^a)</td>
<td>377</td>
<td>Ambulatory patients for Tx evaluation; LVEF 21.8±6.7%</td>
<td>RHC</td>
<td>mPAP &gt;20 mm Hg</td>
<td>62.3%</td>
</tr>
<tr>
<td>Cappola 2002(^a)</td>
<td>1134</td>
<td>New-onset cardiomyopathy; LVEF: N/A</td>
<td>RHC</td>
<td>No a priori definition</td>
<td>46%</td>
</tr>
<tr>
<td>Grigioni 2006(^a)</td>
<td>196</td>
<td>NYHA class III-IV; LVEF 27±9%</td>
<td>RHC</td>
<td>mPAP &gt;25 mm Hg</td>
<td>40.3%</td>
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<td>Shataly 2008(^a)</td>
<td>270</td>
<td>CRT recipients; LVEF 22.6±9.7%</td>
<td>Echo</td>
<td>RVSP &gt;45 mm Hg</td>
<td>34.8%</td>
</tr>
<tr>
<td>Adhyyapak 2010(^a)</td>
<td>147</td>
<td>Ambulatory patients</td>
<td>Echo</td>
<td>RVSP &gt;45 mm Hg</td>
<td>53.7%</td>
</tr>
<tr>
<td>Damy 2010(^4)</td>
<td>270</td>
<td>HF with LVEF ≤45% and measured RVSP</td>
<td>Echo</td>
<td>TR gradient &gt;25 mm Hg</td>
<td>50%</td>
</tr>
<tr>
<td>Miller 2011(^a)</td>
<td>1541</td>
<td>HF with LVEF ≤40%; LVEF 30.5±8.3%</td>
<td>Echo</td>
<td>RVSP &gt;45 mm Hg</td>
<td>34.6%</td>
</tr>
<tr>
<td>Szwajkowski 2012(^27)</td>
<td>1612</td>
<td>LVSD (qualitative), loop diuretics, and measured RVSP</td>
<td>Echo</td>
<td>No a priori definition</td>
<td>47.5%</td>
</tr>
<tr>
<td>Lam 2009(^3)</td>
<td>244</td>
<td>Community inpatients and outpatients; LVEF ≥50%</td>
<td>Echo</td>
<td>RVSP &gt;35 mm Hg</td>
<td>83%</td>
</tr>
<tr>
<td>Leung 2010(^14)</td>
<td>455</td>
<td>Cardiac catheterization registry; LVEDP &gt;15 mm Hg; LVEF ≥50%</td>
<td>RHC</td>
<td>mPAP &gt;25 mm Hg</td>
<td>52.5%</td>
</tr>
<tr>
<td>Damy 2010(^4)</td>
<td>143</td>
<td>HF patients with LVEF &gt;45%, NT-proBNP ≥50 pmol/L, and measured TR</td>
<td>Echo</td>
<td>TR gradient &gt;25 mm Hg</td>
<td>46%</td>
</tr>
<tr>
<td>Tatebe 2011(^3)</td>
<td>676</td>
<td>HF patients NYHA II-I for referred for RHC</td>
<td>RHC</td>
<td>mPAP &gt;25 mm Hg, PCWP &gt;15 mm Hg</td>
<td>23.4%</td>
</tr>
<tr>
<td>Bursi 2012(^5)</td>
<td>1049</td>
<td>Community inpatients and outpatients with HF</td>
<td>Echo</td>
<td>RVSP &gt;35 mm Hg</td>
<td>79%</td>
</tr>
<tr>
<td>Kjaergaard 2007(^7)</td>
<td>388</td>
<td>Admitted for acute HF; LVEF 33 (23–50)%</td>
<td>Echo</td>
<td>No a priori definition</td>
<td>50%</td>
</tr>
<tr>
<td>Khush 2009(^2)</td>
<td>171</td>
<td>Acute HF, clinical trial; SBP ≤125 mm Hg; LVEF ≤30%</td>
<td>RHC</td>
<td>Mixed PH: mPAP ≥25 mm Hg; PCWP &gt;15 mm Hg; PVR &gt;3 WU</td>
<td>47%</td>
</tr>
<tr>
<td>Aronson 2011(^8)</td>
<td>242</td>
<td>Acute HF, clinical trial; LVEF 25±13%</td>
<td>RHC</td>
<td>mPAP &gt;25 mm Hg</td>
<td>76.0%</td>
</tr>
</tbody>
</table>

No a priori definition: investigators presented distribution of measurements without a prespecified cutoff point.

CRT indicates cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-systolic pressure; LVSD, left ventricular systolic dysfunction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; TR, tricuspid regurgitation; Tx, transplantation; and WU, Wood units.
invasive exercise testing can identify truly asymptomatic PH. On the contrary, in patients with HFrEF undergoing invasive cardiopulmonary exercise testing, the decrease in exercise capacity paralleled PH severity. However, 7% of patients did not have exertional symptoms despite severe PH.

Obtaining reliable invasive measurements during exercise is challenging because of wide swings in intrathoracic pressure secondary to increased respiratory rate and tidal volume, technical difficulties, and patients’ inability to maintain peak exercise during hemodynamic acquisition. Therefore, assessment at submaximal exercise might be preferable. Changes in PCWP during graded supine exercise are not linear, because most (>80%) of the increase occurs during the initial exercise stages. In patients with recent HF, when PVR is typically normal or near normal, PAP essentially tracks PCWP during exercise. Thus, assessment at maximal exercise may not be necessary for insights into the mechanism of exercise-induced PH in HF.

Although there are data supporting the value of exercise-induced PH in early diagnosis of PH and prognosis, several aspects are still unclear. Prior studies have evaluated patients with exertional symptoms, and some patients with severe PH may have relatively preserved exercise capacity. Therefore, the value of exercise-induced PH for the diagnostic assessment of dyspnea as an early indicator of PH in asymptomatic patients and as a potential target for treatment in these populations needs further clarification.

Provocative maneuvers, including exercise or saline load, may unmask excessive PAP elevations under mild stress in patients with diastolic dysfunction at risk of HFpEF or with already manifest exercise intolerance and HFpEF. In these patients, the absence of elevated PAP at rest, similar to the absence of other signs of congestion or elevated natriuretic peptide levels, may be less informative than exercise parameters. Thus, PAP elevations with mild exercise in patients with normal pressures at rest could represent a target for future pulmonary vasoactive therapies, assuming that agents lowering PAP during exercise would improve functional capacity and symptoms. However, this hypothesis requires further study.

**PH in Acute HF**

The role of PH in acute HF is less well studied. Hemodynamic worsening is characteristic of acute HF; however, few studies have described the changes over time and the short- and long-term implications of hemodynamics in acute HF. In ambulatory patients, dynamic changes in PAP predict acute HF events, and elevations in 24-hour filling pressures precede episodes of decompensation in both HFrEF and HFpEF patients. Aronson et al reported that before treatment, among 242 patients, only 2 (0.83%) had normal PAP (defined as RHC mPAP ≤25 mm Hg); 59.1% had passive PH (mPAP >25 mm Hg, PCWP >15 mm Hg, and PVR ≤3 WU); and 40.1% had reactive PH (mPAP >25 mm Hg, PCWP >15 mm Hg, and PVR >3 WU). After diuretic and vasoactive therapy for ≤48 hours, passive and reactive PH was present in approximately 25% and 50% of patients, respectively. Patients with persistent reactive PH were classified as fixed PH. A rapidly reversible passive PH component, likely because of pure volume overload, was present in all 3 groups. However, 13% of patients with passive PH during decompensation were classified into the reactive (fixed) PH category at final measurement. Also, 45% of patients with an initial reactive profile had lower PCWP, mPAP, and PVR after treatment, indicating a passive profile. Thus, fixed PH cannot be easily ascertained during acute HF. Further research is needed to identify the neurohumoral and other factors that temporally alter pulmonary vascular function in acute HF. One factor to consider related to the wide variation of the reactive component of PH is the variability of RHC measurements. In a study with serial hemodynamics in patients with pulmonary arterial hypertension, there was wide spontaneous intraindividual variability in PAP, by >20 mm Hg in some patients, with a mean coefficient of variation of 8% in the group. Considering that the progress of HF deteriorates significantly after a hospitalization for decompensated HF, it would be reasonable to consider and investigate all the abnormalities that are present during decompensation, including hemodynamic abnormalities. This could help us identify potential clues for the accelerated deterioration with the ultimate goal to intervene and delay the progress of HF.

**Conclusions**

Secondary PH is highly prevalent among patients with HF regardless of LVEF. Although varying definitions lead to varying estimates of PH prevalence in HF, especially in echocardiographic studies at the population level, the proportion of HF patients with PH increases with HF severity and ranges from 25% to >50% in referred populations. A persistently elevated TPG and PVR after treatment optimization and reduction of PCWP in patients with HF may indicate structural changes in the pulmonary vascular bed, and these patients may benefit from pulmonary vasoactive agents. The role of exercise-induced PH and the response of PAP during acute HF treatment need further elucidation.

**Disclosures**

Dr. Gheorghiade has been a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer HealthCare AG, CorThera, Cytokinetics, Debiopharm S.A., Errekappa Therapeutics, GlaxoSmithKline, Ikaria, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda Pharmaceutical, and Trevena Therapeutics. Dr. Butler has been a consultant for Ono Pharma, Trevena, Bayer, and Amgen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**References**


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