Epidemiology of Pulmonary Hypertension and Right Ventricular Failure in Left Heart Failure

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Abstract Pulmonary hypertension (PH) leading to right ventricular failure (RVF) is a common complication of left heart failure irrespective of the left ventricular ejection fraction. PH due to left heart disease is the most common cause of PH. The prevalence of PH and RVF in left heart failure varies depending on the patient population studied, the method used to diagnose PH, and the hemodynamic criteria used to define PH. Elevated left-sided filling pressure and functional mitral regurgitation are the two major determinants of PH in left heart failure. PH is associated with markers of disease severity, advanced symptoms, and worse long-term outcomes including heart failure hospitalization and mortality in left heart failure. RVF has independent, incremental prognostic value over PH for adverse outcomes in left heart failure. PH and RVF may be potential therapeutic targets in patients with left heart failure.

Keywords Heart failure · Valvular heart disease · Pulmonary venous hypertension · Prognosis · Right ventricular dysfunction

Introduction

Pulmonary hypertension (PH) is a common complication of left heart failure. PH due to left heart disease is more prevalent than other World Health Organization (WHO) categories of PH [1]. Moreover, the prevalence of PH due to left heart disease will likely expand as the incidence of left heart failure continues to increase in a growing elderly population [2]. Elevated left ventricular filling pressure leading to reactive pulmonary arterial vasoconstriction and pulmonary vascular remodeling results in PH in left heart failure [3•]. The presence of PH increases the resistive and the pulsatile afterload of the right ventricle, ultimately leading to right ventricular failure (RVF) [4]. The coexistence of PH and RVF in left heart failure is associated with markers of disease severity, advanced symptoms, and worse long-term outcomes. In this article, we review the prevalence, determinants, and prognostic value of PH and RVF in left heart failure, specifically in heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and left-sided valvular heart disease.

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Classification of PH Due to Left Heart Failure

PH due to left heart disease is defined as mean pulmonary artery pressure (PAP) ≥25 mmHg in the presence of pulmonary artery wedge pressure (PAWP) >15 mmHg [5]. It is further classified into subtypes depending on the presence of intrinsic pulmonary vascular disease (pre-capillary component) in addition to the elevated left-sided filling pressures (post-capillary component). Due to a lack of consensus, various classification systems have been used in the literature based on different hemodynamic criteria (Table 1).

Table 1 Classification of PH due to left heart failure

Classification/nomenclature	Hemodynamic criteria
Pulmonary venous hypertension or passive PH, or post-capillary PH	MPAP≥25 mmHg
	PCWP/LVEDP>15 mmHg
	TPG<12–15 mmHg and PVR<3 WU
Mixed PVH or PH out of proportion to left-sided filling pressures	MPAP≥25 mmHg
	PCWP/LVEDP>15 mmHg
	TPG>12–15 mmHg or PVR>3 WU
Isolated post-capillary PH	MPAP≥25 mmHg
	PCWP/LVEDP>15 mmHg
	DPG<7 mmHg
Combined pre- and post-capillary PH	MPAP≥25 mmHg
	PCWP/LVEDP>15 mmHg
	DPG≥7 mmHg

PH pulmonary hypertension, *MPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *LVEDP* left ventricular end diastolic pressure, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance, *WU* wood units, *PVH* pulmonary venous hypertension, *DPG* diastolic pulmonary pressure gradient

Post-capillary PH

Elevated left-sided filling pressure leads to an obligatory, passive increase in PAP in order to maintain forward flow. Typically, this increase in PAP is proportionate to the elevated left-sided filling pressure and it normalizes with reduction in the left-sided filling pressure. At this stage, due to the absence of a pre-capillary component, both the transpulmonary gradient (TPG, the difference between mean PAP and PAWP) and the pulmonary vascular resistance (PVR) remain within normal limits (TPG<12–15 mmHg and PVR<2.5–3 Wood units (WU)). This stage of PH in left heart disease has been described in the literature using various nomenclatures including pulmonary venous hypertension, passive PH, or post-capillary PH [6]. For the purpose of this review, we will refer to this as post-capillary PH.

Mixed PH (Pre- and Post-capillary PH)

Over time, the elevated left-sided filling pressure triggers pulmonary arterial vasoconstriction. This is later followed by intrinsic pulmonary arteriolar remodeling due to decreased nitric oxide availability and increased endothelin expression [7, 8]. The superimposed pre-capillary component increases the PAP disproportionate to the left-sided filling pressure, resulting in an elevated TPG (>12–15 mmHg) and/or PVR (>2.5–3 WU). This is referred to as mixed PH (post- and pre-capillary component) or PH out of proportion to the left-sided filling pressures [6]. We will refer to this as mixed PH for the purpose of this review.

Isolated Post-capillary vs. Combined Post- and Pre-capillary PH

Traditionally, elevated TPG (>12–15 mmHg) or PVR (>2.5–3 WU) has been used to delineate the presence of a pre-capillary component in PH due to left heart disease [9•]. However, growing evidence suggests that both TPG and PVR are flow dependent and may not accurately reflect the presence of intrinsic pulmonary arteriolar remodeling [10••]. In contrast to TPG and PVR, diastolic pulmonary vascular pressure gradient (DPG, the difference between diastolic pulmonary artery pressure and pulmonary artery wedge pressure) is not flow dependent and more accurately identifies the presence of pre-capillary pulmonary arteriolar remodeling [11]. Hence, the most recent, fifth world symposium on PH proposed a new classification and hemodynamic definition for PH due to left heart disease based on DPG (Table 1): isolated post-capillary (DPG<7 mmHg) and combined post-capillary and pre-capillary PH (DPG≥7 mmHg) (Fig. 1) [12••].

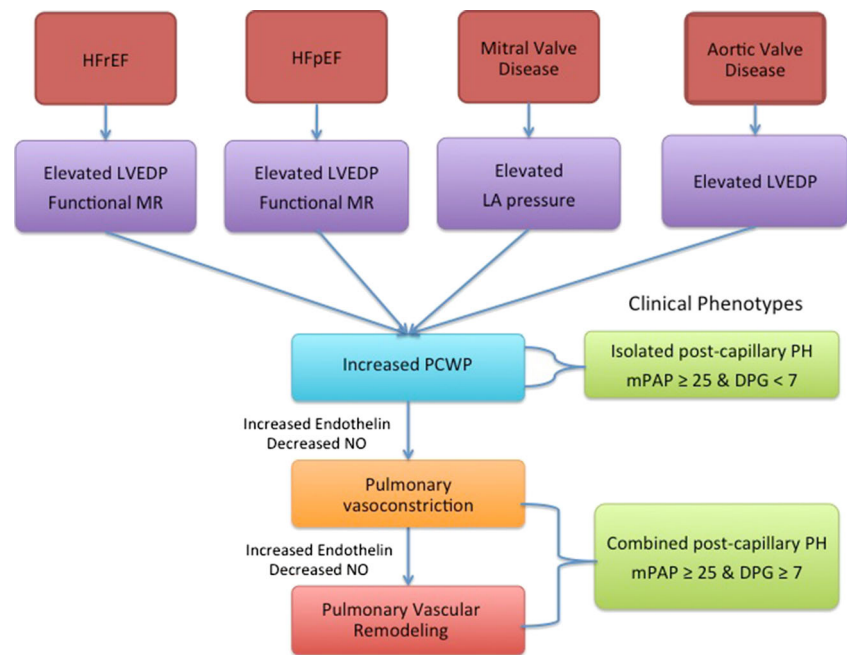## PH and Right Ventricular Dysfunction in HFrEF

Prevalence of PH and Right Ventricular Dysfunction in HFrEF

The prevalence of PH and RVF failure in HFrEF varies depending on the patient population studied (ambulatory vs. hospitalized for decompensated heart failure), the method (echocardiography or right heart catheterization) used to diagnose PH, and the hemodynamic criteria used to define PH.

The prevalence of PH based on echocardiography varies from 35 to 47.5 % (Table 2). In a retrospective review of 1,541 stable ambulatory HFrEF patients with an ejection fraction <40 % from the Mayo Clinic, 35 % of the patients had a right ventricular systolic pressure (RVSP) >45 mmHg [13]. In a more recent retrospective, population-based longitudinal cohort study in Scotland, RVSP >45 mmHg was present in 47.5 % of HFrEF patients [14].

The prevalence of PH based on invasive hemodynamic assessment in HFrEF varies from 33 to 46 % (Table 2). In 450 ambulatory HFrEF patients referred for right heart catheterization, 33 % of the patients had a mean PAP >25 mmHg [15•]. Of the 1,134 patients evaluated for new onset cardiomyopathy at the Johns Hopkins Hospital, 46 % of patients had a mean PAP >25 mmHg [16]. In a different study of 320 ambulatory HFrEF patients who had right heart catheterization as a part of transplant evaluation, 36 % had mixed PH with a PVR >2.5 WU [17]. A recent retrospective review from the Mayo Clinic reported that 40 % of the HFrEF patients referred for invasive hemodynamic assessment had mixed PH with a PVR >3 WU [15•].

Fig. 1 Mechanism of pulmonary hypertension in left heart failure. *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LVEDP* left ventricular end diastolic pressure, *MR* mitral regurgitation, *LA* left atrium, *PCWP* pulmonary capillary wedge pressure, *PH* pulmonary hypertension, *mPAP* mean pulmonary artery pressure, and *DPG* diastolic pulmonary gradient

Determinants of PH and Right Ventricular Dysfunction in HFrEF

The two major determinants of PH in patients with HFrEF are elevated left-sided filling pressure and functional mitral regurgitation (Fig. 1). The severity of PH correlates directly with the severity of echo-derived indices of left-sided filling pressure (mitral valve E/E′ ratio and deceleration time) and the severity of functional mitral regurgitation based on the mitral regurgitant orifice area rather than the left ventricular ejection fraction [18••, 19, 20]. In a single center series of 388 patients (75 % with left ventricular ejection fraction <50 %), HFrEF patients with a left ventricular restrictive filling pattern had a higher systolic PAP compared to those with a non-restrictive filling pattern (41 vs. 37 mmHg, $P<0.02$) [21]. Furthermore, age, female gender, left atrial enlargement, atrial fibrillation, and decreased pulmonary artery compliance have been correlated with the presence of PH in HFrEF [15•, 22]. Finally, polymorphism in the promoter region of the serotonin transporter gene has also been associated with the presence of PH in HFrEF patients. HFrEF patients with the homozygous long variant (LL) had a higher PAP compared to those with the homozygous short variant (SS) or heterozygous variant (SL) [23].

Prognostic Value of PH and Right Ventricular Dysfunction in HFrEF

Several studies have consistently associated echocardiography-derived indices of PH, estimated systolic PAP and tricuspid regurgitant velocity, with increased mortality in HFrEF. In a recent study of 419 ambulatory HFrEF patients followed for a median of 2.6 years, echocardiography-estimated systolic PAP ≥48 mmHg was associated with a threefold higher risk of death, cardiac transplantation, left ventricular assist device implantation, or heart failure hospitalization [24]. Similarly, a community-based study from Olmsted County, MN, reported a linear relationship between echocardiography-estimated systolic PAP and long-term all-cause mortality [25].

The presence of mixed PH is associated with a higher risk of adverse outcomes compared to post-capillary PH. Miller et al. studied 463 stable ambulatory HFrEF patients referred for invasive hemodynamic assessment [15•]. Over a median follow-up of 2.1 years, patients with mean PAP >25 mmHg had a twofold higher risk of death compared to those without PH. Among those with PH, patients with mixed PH demonstrated a 1.5-fold higher risk of death compared to those with post-capillary PH. In this study, PVR >4 WU and pulmonary artery compliance <2.0 ml/mmHg were the strongest independent predictors of death [15•]. Likewise, in a different study from the Johns Hopkins Hospital, the risk of death increased significantly in patients with HFrEF when PVR increased beyond three WU [16].

Change in PAP over time provides additional prognostic information on HFrEF. An increase in mean PAP over time in serial hemodynamic assessments was independently associated with an increased risk of death in patients with HFrEF [26]. Interestingly, in corollary, a reduction in estimated systolic PAP with cardiac resynchronization therapy in HFrEF patients was associated with a reduction in death, cardiac transplantation, or heart failure-related hospitalizations [27].

Table 2 Prevalence of PH and right ventricular dysfunction in left heart failure

Population	Diagnostic modality	Definition of PH or RV dysfunction	Prevalence
HFrEF	Echo	Doppler-estimated RVSP>45 mmHg	35–47.5 % [13, 14]
	RHC	Mean PAP>25 mmHg	33–46 % [15•, 16]
		PVR>2.5–3 WU	36–40 % [15•, 17]
HFpEF	Echo	Doppler-estimated systolic PAP>35–45 mmHg	18–83 % [18••, 30–32]
	Echo	PVR>2.5 WU	11 % [32]
	Echo	RVFAC<35 %	4–33 % [32, 33•, 34, 35]
Mitral stenosis	Echo	Doppler-estimated systolic PAP>50 mmHg	41 % [46]
	RHC	Mean PAP>25 mmHg	73 % [45]
		TPG>15 mmHg	19 % [45]
		PVR>6 Units	26 % [47]
Mitral regurgitation	Echo	Doppler-estimated systolic PAP>50 mmHg	23 % [48]
	RHC	Mean PAP>30 mmHg	76 % [49]
		Mean PAP>50 mmHg	44 % [49]
Aortic stenosis	RHC	Systolic PAP>50 mmHg	15–29 % [51–53]
Aortic regurgitation	Echo	Doppler-estimated systolic PAP>60 mmHg	16 % [55]

PH pulmonary hypertension, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *RVSP* right ventricular systolic pressure, *RHC* right heart catheterization, *PAP* pulmonary artery pressure, *RVFAC* right ventricular fractional area change, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance, *WU* wood units, *PVH* pulmonary venous hypertension, *DPG* diastolic pulmonary pressure gradient

The prognostic importance of PH in HFrEF varies depending on the underlying etiology of the left ventricular systolic dysfunction. The risk of death associated with the presence of PH is much higher in patients with myocarditis compared to those with ischemic or non-ischemic cardiomyopathy [16]. In a study of 1,134 patients with cardiomyopathies of varying etiologies, over a median follow-up of 4.4 years, the hazard ratio of death increased by 25 % for each 5 mmHg increase in mean PAP in the total cohort. However, in patients with myocarditis, for the same 5 mmHg increase in mean PAP, the hazard ratio for death increased remarkably by 85 % [16].

The presence of RVF has incremental prognostic value over PH for adverse outcomes in HFrEF [28, 29]. Right ventricular fractional area change (RVFAC) <35 % was associated with a twofold increased risk of death, cardiac transplantation, left ventricular assist device implantation, or heart failure hospitalization independent of elevated systolic PAP [24].

Epidemiology of PH and Right Ventricular Dysfunction in HFpEF

Prevalence of PH and Right Ventricular Dysfunction in HFpEF

PH is more prevalent in HFpEF than in HFrEF. The prevalence of PH in HFpEF varies from 18 to 83 % depending on the patient population studied and the cutoff value of estimated systolic PAP used to define PH (Table 2). In a population-based study of 244 HFpEF patients in Olmsted County, MN, 83 % of the patients had estimated systolic PAP >35 mmHg [30]. The median estimated systolic PAP in this cohort was 48 mmHg (IQR 37–56). However, in a UK-based study of 354 consecutive HFpEF patients referred to a heart failure clinic, only 18 % had a RVSP >35 mmHg, which is equivalent to an estimated systolic PAP of >45 mmHg [18••]. In HFpEF patients hospitalized for heart failure exacerbation in New York, the mean estimated systolic PAP was 47±14 mmHg [31]. In the echocardiographic substudy of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), 450 patients had a measurable tricuspid regurgitant jet velocity [32]. Of these 450 patients, 36 % had a tricuspid regurgitant jet velocity >2.9 m/s (equivalent to an estimated systolic PAP of at least 35 mmHg+right atrial pressure) and 11 % had a PVR >2.5 WU.

The data on the prevalence of RVF in HFpEF is limited. In the echocardiographic substudy of the TOPCAT trial, 31 % of the patients had a RVFAC <45 %, 11 % had a RVFAC <40 %, and 4 % had a RVFAC <35 % [32]. In a recent study of 96 HFpEF patients referred to the Mayo Clinic Cardiac Catheterization Laboratory, 33 % of the patients had RVFAC <35 % [33•]. Puwanant et al. reported a similar prevalence of 33 % right ventricular dysfunction in patients with HFpEF [34]. In this study, HFpEF patients had a better right ventricular function based on RVFAC, tricuspid annular plane systolic excursion (TAPSE), and peak systolic tricuspid annular tissue velocity (S') compared to HFrEF patients. In a prospective study of 419 HFpEF patients referred to a single tertiary medical center, 34 % had right

ventricular hypertrophy, 28 % had TAPSE <18 mm, and 15 % had RVFAC <35 % [35].

Determinant of PH and Right Ventricular Dysfunction in HFpEF

Similar to HFrEF, elevated left-sided filling pressure due to left ventricular diastolic dysfunction is the predominant determinant of PH in patients with HFpEF (Fig. 1). Lam et al. reported a linear correlation between estimated systolic PAP and PAWP estimated based on the mitral E/E' ratio (r=0.21; P<0.007) [30]. Another echocardiography-based study of 69 patients with HFpEF also reported a strong correlation between estimated systolic PAP and PAWP (r=0.73) [36]. In this study, HFpEF patients with a restrictive physiology of the left ventricle had a higher systolic PAP compared to those with a non-restrictive pattern. PH has also been associated with the presence of functional mitral regurgitation in HFpEF [37].

The risk factors that predispose to the development of mixed PH in HFpEF are unclear. Several possible factors have been proposed. First, age is considered a risk factor for the development of mixed PH in HFpEF, as older persons are more prone to develop arterial stiffening in the systemic as well as the pulmonary circulation [38]. Systolic PAP has been shown to increase with increasing age [39]. Also, HFpEF patients with PH are more likely to be older compared to those without PH [30]. Second, female gender is another potential risk factor. In 676 consecutive HFpEF patients referred to a single center, female gender was the only independent predictor of mixed PH (odds ratio 2.12, 95 % confidence interval (CI) 1.05–4.30, P=0.03) [22]. The exact reason behind this association is unclear. Systemic arterial stiffness increases with age more commonly in women; hence, older women are more likely to have increased pulmonary artery stiffness [40–42]. Finally, obesity, atrial arrhythmias, and chronic obstructive lung disease have been associated with increased risk of developing PH in patients with HFpEF [43].

Melenovsky et al. reported correlates of right ventricular dysfunction in HFpEF in 96 patients with HFpEF who had simultaneous right heart catheterization and echocardiogram within 48 h. In this study, right ventricular dysfunction was more common in men than in women despite similar severity of PH. In addition, patients in atrial fibrillation were more likely to have right ventricular dysfunction compared to those in sinus rhythm. Other factors independently associated with right ventricular dysfunction were systolic PAP, presence of coronary artery disease, lower systemic arterial pressures, and lower left ventricular ejection fraction.

Prognostic Value of PH and RVF in HFpEF

The presence of PH is associated with increased mortality in HFpEF. In the study by Lam et al., over a median follow-up of 2.8 years, every 10 mmHg increase in estimated systolic PAP was associated with a 1.2-fold increased risk of death independent of age [30]. In the same study, HFpEF patients with an estimated systolic PAP >48 mmHg had a higher mortality compared to those with an estimated systolic PAP <48 mmHg. Likewise, in the Danish prospective placebo-controlled multicenter Echocardiography and Heart Outcome Study (ECHOS), of the 97 patients with HFpEF who had a good-quality tricuspid regurgitation jet velocity, patients with estimated systolic PAP >39 mmHg had an increased mortality compared to those with estimated systolic PAP <39 mmHg [21]. In a prospective study of 334 patients with PH due to left heart disease, of which 90 % had HFpEF, 1-year survival was 82 % and 2-year survival was only 74 % [44].

Similar to HFrEF, the presence of right ventricular dysfunction is associated with independent incremental risk for adverse outcomes over PH in HFpEF. HFpEF patients with RVFAC <35 % have an increased risk of death compared to patients without right ventricular dysfunction (RVFAC≥35 %) regardless of systolic PAP [33•]. In a recent study of 419 HFpEF patients prospectively followed for a median follow-up of 18 months, the presence of right ventricular remodeling was a strong predictor of mortality. In this study, every 1 standard deviation increase in right ventricular wall thickness was associated with a 1.4-fold increased risk of death [35].

PH and Right Ventricular Dysfunction in Left-Sided Valvular Heart Disease

Mitral Valve Disease

PH frequently complicates both mitral stenosis and mitral regurgitation (Table 2). In a recent series of 314 patients with isolated mitral stenosis undergoing percutaneous mitral balloon commissurotomy, 73 % had a mean PAP >25 mmHg and 19 % had a TPG >15 mmHg [45]. In a different, single center series of 559 patients who underwent percutaneous mitral balloon valvotomy, 41 % had invasively measured systolic PAP >50 mmHg [46]. In an early series of 58 patients with isolated mitral stenosis who underwent mitral valvotomy, 26 % of patients had a PVR >6 WU [47].

In a more recent multicenter international registry of 459 patients with isolated mitral regurgitation due to filial mitral leaflets, 23 % of patients had Doppler-estimated systolic PAP >50 mmHg [48]. Alexopoulos et al. studied 41 patients with isolated mitral regurgitation who had invasive right heart hemodynamics [49].

In this series, 76 % of the patients had a mean PAP >30 mmHg and 44 % had a mean PAP >50 mmHg.

The presence of PH depicts poor prognosis in patients with mitral valve disease. In the multicenter international mitral regurgitation registry, over a median follow-up of 4 years, systolic PAP >50 mmHg was associated with increased risk of all-cause mortality, cardiovascular mortality, and heart failure [48]. In addition, PH was associated with increased risk of early 30-day mortality and heart failure after surgical mitral valve replacement. In a large single center series of 2,316 patients who underwent mitral valve replacement for either mitral stenosis or regurgitation (2:1 ratio), patients with systolic PAP >50 mmHg had a higher 30-day mortality compared to those with systolic PAP <50 mmHg (10.6 vs. 3.6 %) [50]. However, in this study, there was no difference in long-term outcomes between those with and without PH.

Aortic Valve Disease

PH is common in isolated aortic stenosis. The prevalence of PH defined as invasively measured systolic PAP >50 mmHg varies from 15 to 29 % (Table 2) [51–53]. The severity of PH in aortic stenosis correlates with the severity of diastolic dysfunction and the elevation in left ventricular end diastolic pressure as opposed to the aortic valve area [54, 55]. PH is less common in aortic regurgitation when compared to other valvular heart diseases. In a series of 506 patients with aortic regurgitation, Doppler-estimated systolic PAP >60 mmHg was noted in approximately 16 % of patients with severe aortic regurgitation and it was associated with left ventricular enlargement and functional mitral regurgitation [56].

In patients with severe aortic stenosis, elevated systolic PAP is associated with increased mortality [57]. Elevated systolic PAP also increases the early 30-day and long-term mortality after surgical aortic valve replacement [58–60]. Systolic PAP >60 mmHg was also associated with increased early and long-term mortality after transcatheter aortic valve replacement [61, 62]. However, in one study, transcatheter aortic valve replacement was associated only with an increased 1-year mortality, but not with increased 30-day mortality [63].

Conclusion

PH and RVD are common in left heart failure; however, the exact prevalence is not known due to the heterogeneity in the diagnostic criteria used and the patient population studied. Regardless of the underlying etiology, the presence of PH depicts poor prognosis in patients with left heart failure.

Compliance with Ethics Guidelines

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