Management of Pulmonary Hypertension
Associated with Left Heart Disease

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KEYWORDS

• Hypertension • Heart failure • Ejection fraction • Right ventricular • Pulmonary hypertension
• Pulmonary arterial hypertension

KEY POINTS

- Pulmonary hypertension (PH) due to left heart disease, or WHO group 2 PH, is the most frequent cause of PH.
- Long-standing PH results in right heart strain and failure, which further worsen symptoms and prognosis.
- The goal is to identify and treat the disease before onset of fixed pulmonary arterial hypertension and right heart failure.

INTRODUCTION

Pulmonary hypertension (PH) due to left heart disease, or WHO group 2 PH, is the most frequent cause of PH. It affects approximately 50% to 60% of patients with heart failure with preserved ejection fraction (HFpEF) as well as 60% of those with heart failure with reduced ejection fraction (HFrEF),[1,2] particularly advanced stages of disease, and contributes significantly to disease progression and unfavorable outcomes.

Elevated left-sided filling pressures secondary to diastolic or systolic dysfunction or valvular lesions (especially mitral valve disease) eventually result in postcapillary PH. Venous hypertension is back transmitted via capillaries to the pulmonary arterial system initially in a passive fashion resulting in passive pulmonary arterial hypertension.[3–5] During the passive phase, diuresing the patient is likely to result in complete normalization of pulmonary pressures. Over time, long-standing passive PH results in pulmonary arterial endothelial dysfunction, leading to elevated levels of endothelin 1 (ET-1), decreased nitric oxide level, and decrease in brain natriuretic peptide–mediated vasodilatation.[6,7] These biochemical changes result in active pulmonary arterial vasospasm, leading to further increase in pulmonary arterial pressures.

Eventually, pulmonary vascular remodeling is associated with fibrosis and decreased vascular compliance resulting in fixed elevation in pulmonary arterial pressures independent of the pressure changes in the left heart, no longer amenable to reversal with resolution of the underlying HF. Severity of PH is usually directly proportional to severity of underlying heart failure or valvular disease. Long-standing PH results in right heart strain and failure, which further worsen symptoms and prognosis. In view of the natural history of the disease, early diagnosis and management of volume overload is the key to favorable outcomes. The goal is to identify and treat the disease before onset of fixed pulmonary arterial hypertension and right heart failure.

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HEMODYNAMIC DEFINITIONS

PH is defined hemodynamically by right heart catheterization, by a mean pulmonary arterial pressure (PAP) greater than or equal to 25 mm Hg at rest.[3] Pulmonary artery wedge pressure (PAWP) distinguishes precapillary (≤15 mm Hg) and postcapillary (>15 mm Hg) PH in setting of normal or reduced left ventricular ejection fraction. As a consequence of these pressure cutoffs, the transpulmonary gradient (TPG = mean PAP − PAWP) has been used clinically for many years to distinguish between "passive" PH (TPG <12 mm Hg) and "reactive" PH (TPG ≥12 mm Hg).[3,8]

Patients with TPG greater than or equal to 12 mm Hg, also called to have "out of proportion" PH and assumed to have pulmonary pressures over that, can be explained by passive back transmission of elevated left heart pressures. However, the term "out of proportion" PH is challenging to interpret and could be unpredictable clinically. We should not assume that a high TPG represents superimposed pulmonary arterial hypertension because that is not always the clinical scenario.[9] For example, patients with HFrEF who were diagnosed with "reactive PH," unresponsive to vasodilator challenge, can completely normalize their pulmonary pressures solely by treatment of their left-sided HF with a left ventricular assist device (LVAD). The TPG depends flow rate and varies with stroke volume and cardiac output. The dependence of TPG on pulmonary vascular flow, resistance, and left heart filling pressures (PAWP) makes it a poor measure of pulmonary arterial vascular disease in the setting of left heart disease.[3,9]

The Fifth World Symposium in Pulmonary Hypertension from Nice, France took place in 2013. The use of the term "out of proportion" PH was discouraged.[5] Experts recommended the use of the diastolic pressure gradient (DPG = diastolic PAP − PAWP), rather than TPG, to better assess the development of pulmonary vascular disease in patients with left heart disease. Diastolic PAP is less sensitive to changes in pulmonary vascular flow rate (stroke volume/cardiac output), resistance, and PAWP.[4,9] It has been shown to be a less sensitive to pulmonary vascular distensibility. A study correlating PH with histology has demonstrated that DPG has a higher specificity to identify significant pulmonary vascular disease.[10]

The normal upper limit of DPG was assumed to be 5 mm Hg,[4] as derived from athletic young adults. The DPG was revisited by Gerges and colleagues[10] in a study of 2056 patients with HF. PH, defined by mean pulmonary arterial pressure (mPAP) greater than 25 mm Hg, was diagnosed in 1094 of these patients, a TPG greater than 12 mm Hg was diagnosed in 490, and a combination of TPG greater than 12 mm Hg and a DPG greater than 7 mm Hg in 179 (16%). Normal DPG values range from 1 to 3 mm Hg and remains less than 5 mm Hg in most patients with cardiac disease (excluding shunts).[9,11] Elevated DPG is a marker of pulmonary vascular remodeling. Studies correlating DPG with pulmonary vascular resistance (PVR) have shown that individuals with DPG less than 5 mm Hg are unlikely to have severe pulmonary vascular disease. A PAWP greater than 15 mm Hg with a DPG less than 7 mm Hg is more likely associated with isolated postcapillary PH, previously called "passive PH." Individuals with PAWP greater than 15 mm Hg with a DPG greater than or equal to 7 mm Hg have combined pre- and postcapillary PH, previously called "out of proportion PH" or "reactive PH"[3,10,12] (**Table 1**).

Elevated DPG has been shown to have prognostic value.[10] The survival of the patients with high TPG and DPG was very poor compared with that of patients with untreated pulmonary arterial hypertension. Some histopathologic examinations of the pulmonary small vessels in patients with both increased TPG and DPG have shown pulmonary vascular remodeling with medial hypertrophy, intimal thickening, and adventitial proliferation. From multivariate analysis, the DPG emerged as an independent predictor of survival, with a cutoff value of 7 mm Hg.[10] Patients with TPG greater than 12 mm Hg and diastolic pressure difference (DPD) greater than 7 mm Hg have a median survival of ∼6.5 years. Patients with DPD less than

Table 1
Fifth World Symposium in Pulmonary Hypertension—classification of pulmonary hypertension due to left heart failure

PH-LHD	Mean PAP	PAWP	DPG	PVR
Isolated postcapillary PH	≥25 mm Hg	>15 mm Hg	<7 mm Hg	≤3 WU
Combined pre- and postcapillary PH	≥25 mm Hg	>15 mm Hg	≥7 mm Hg	>3 WU

Abbreviations: LHD, left heart disease; WU, Wood units.
Data from Refs.[3,5,10]