LEFT HEART DISEASE AND PULMONARY HYPERTENSION: CONTROVERSY REDEFINED

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Left heart disease (LHD) is the most prevalent cause of pulmonary hypertension (PH) and can be due to systolic or diastolic dysfunction or valvular heart disease. Regardless of the cause, the common mechanism of PH associated with LHD is elevated left atrial pressure that leads to a passive increase in pulmonary pressure. In some patients, additional components such as endothelial dysfunction (due to a decrease in nitric oxide and increase in endothelin-1) and vasoconstriction result in vascular remodeling, leading to further increases in pulmonary artery pressure (PAP) and right ventricular failure. When present, PH is associated with a worse prognosis in patients with LHD.[1]

Significant advances have been achieved in the treatment of pulmonary arterial hypertension (PAH), including 14 different therapies that target 4 different pathways. While these treatments have improved the quality of life and survival for patients with PAH, there are currently no approved therapies for those with PH due to LHD (PH-LHD). Several drugs have undergone clinical trials targeting heart failure patients with or without PH, all with disappointing results. One explanation is believed to be the inherent difficulty in defining the right population. This highlights one of the major challenges in PH-LHD: that is, how to appropriately classify patients hemodynamically to best reflect the changes occurring in the pulmonary vasculature. Pulmonary hypertension is defined as a mean PAP (mPAP) ≥ 25 mm Hg, with PAH including pulmonary artery wedge pressure (PAWP) < 15 mm Hg and pulmonary vascular resistance (PVR) ≥ 3 Wood units. For PH-LHD, a PAWP ≥ 15 mm Hg is required along with an mPAP ≥ 25 mm Hg. The challenge, however, is with patients who have a mixture of both pre- and postcapillary PH due to the progression of pulmonary vascular remodeling. This group has been commonly referred to as "mixed PH" or "out-of-proportion PH," and the common hemodynamic markers used to define this group are transpulmonary gradient (TPG: mPAP - PAWP) ≥ 12 mm Hg and/or PVR ≥ 3 Wood units.[2]

During the Fifth World Symposium on Pulmonary Hypertension, the two following recommendations were instituted. First, in order to form a cohesive terminology, the term "combined postcapillary and precapillary PH" (Cpc-PH) should be used in place of "out-of-proportion PH."[1] Second, it was recommended that diastolic pulmonary gradient (DPG: diastolic PAP - PAWP) be used in lieu of TPG as the hemodynamic marker for PH-LHD since the diastolic PAP is less influenced by the PAWP and stroke volume compared to TPG. This recommendation was based on a study by Gerges et al. demonstrating that a TPG ≥ 12 mm Hg and a DPG ≥ 7 mm Hg was predictive of outcome in patients with postcapillary PH.[3] The discussion points also focused on the importance of performing a skilled right heart catheterization with attention paid to obtaining the PAWP at the physiologically optimal point.

In subsequent studies, the DPG failed to serve as a predictive marker in the heart failure population. Furthermore, a low DPG also appears to correlate with outcome, thus a "U-shaped" relationship seems to apply in evaluating DPG and PH-LHD.[4] Based on the collective data, the European Society of Cardiology/European Respiratory Society established a guideline recommending that patients with Cpc-PH adhere to the criteria of DPG ≥ 7 mm Hg and/or PVR > 3 Wood units (Table 1).[5]

References

1. Vachiéry JL, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart disease. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D101-8.

Definition	Characteristics (measured at rest)	Clinical Group(s)
PH	mPAP ≥ 25 mm Hg	All
Precapillary PH	mPAP ≥ 25 mm Hg PAWP ≤ 15 mm Hg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Postcapillary PH	mPAP ≥ 25 mm Hg PAWP > 15 mm Hg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated postcapillary PH (Ipc-PH)	DPG < 7 mm Hg and/or PVR ≤ 3 WU	
Combined postcapillary and precapillary PH (Cpc-PH)	DPG ≥ 7 mm Hg and/or PVR > 3 WU	

Table 1. Hemodynamic definitions of pulmonary hypertension.[5]
CO: cardiac output; DPG: diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WU: Wood units.

2. Fang JC, DeMarco T, Givertz MM, et al. World Health Organization Pulmonary Hypertension group 2: pulmonary hypertension due to left heart disease in the adult--a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. J Heart and Lung Transplant. 2012 Sep;31(9):913-33.
3. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013 Mar;143(3):758-66.
4. Naeije R, Vachiéry JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013 Jan;41(1):217-23.
5. Galiè N, Humbert M, Vachiéry JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119.