Pulmonary Hypertension and Heart Failure
A Dangerous Liaison

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KEYWORDS

• Pulmonary hypertension • Heart failure • Mean pulmonary artery pressure • Left atrial pressure
• Right heart dysfunction • Pulmonary vascular resistance

KEY POINTS

- Pulmonary hypertension (PH) due to heart failure, classified as Group 2, is the most common form.
- Group 2 PH occurs secondary to left ventricular systolic dysfunction, diastolic dysfunction, and/or left-sided valvular disease, all conditions that promote an increase in left atrial pressure, transmitted backward to the pulmonary veins, capillaries, and arteries.
- The hemodynamic cascade from left to right typical of this condition favors right heart dysfunction, which is a turn point that signals unfavorable prognosis.
- No disease-specific therapies currently exist.

DEFINITION AND CLASSIFICATION

Pulmonary hypertension (PH) due to heart failure (HF), otherwise defined as Group 2, according to recent guidelines, is the most frequent form of PH.[1]

A thorough hemodynamic definition of Group 2 PH is challenging due to its variable progression and precipitating factors, as well as to the complex pathobiological changes involving the pulmonary veins, capillaries, and small arteries evolving nature that mediate the transition from a pure passive backward left atrial pressure (LAP) transmission to the development of a precapillary component.

Although there is agreement in the background definition of left-sided PH as a mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg at rest along with a pulmonary artery wedge pressure (PAWP) >15 mm Hg, assessed by right heart catheterization (RHC),[1] uncertainty and confusion exist for a correct staging of the disease, matching hemodynamics to underlying vascular dearrangement.[2] Thus, the "optimal" hemodynamic definition should link the underlying left heart disease to vascular pathology reflecting disease severity and clinical outcome.[3]

In the attempt to bring consistency, the 5th World Symposium on PH in Nice, 2013, proposed a new nomenclature based on 2 definitions: "isolated postcapillary PH" (Ipc-PH) and "combined postcapillary and precapillary PH" (Cpc-PH), introducing the measure of diastolic pressure gradient (DPG: diastolic pulmonary pressure-PAWP) as a potential optimal measure for defining vascular involvement.[4] This proposal was thought to be simple and comprehensive enough to overcome the previous identified drawbacks in using the transpulmonary gradient (TPG: mPAP-PAWP), a parameter highly dependent on cardiac output changes with its related definition of PH "out of proportion." Because pulmonary vascular resistance (PVR) is affected by cardiac output as well, this measure was removed.

Therefore, a final classification of Group 2 PH required a DPG $\leq$7 mm Hg and a DPG greater than 7 mm Hg for Ipc-PH and Cpc-PH, respectively.

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Because DPG was confirmed to be of some pathophysiological relevance but disappointing *on* clinical and prognostic impact, some problems have emerged on the potential to fully characterize left-sided PH by DPG[5,6] and a few corrections were prompted in the European Society of Cardiology/European Respirator Society (ESC/ERS) Guidelines in 2015. PVR (>3 Wood units [WU]) was reintroduced in alternative or in combination with DPG greater than 7 mm Hg.[1]

According to these changes, most recent findings have pointed out the strong prognostic power of PVR greater than 3 WU in isolation and with a DPG $\leq$7 mm Hg or in combination with a DPG greater than 7 mm Hg.[7] Even more, no difference in survival has been reported between patients at an intermediate stage of hemodynamic impairment (PVR >3 WU and DPG <7 mm Hg) versus patients with Cpc-PH (PVR >3 WU and DPG >7 mm Hg),[7] considering that the vast majority of patients with a DPG >7 mm Hg have already developed a PVR >3 WU.[7]

In parallel to these observations, there has been a series of reports addressing pulmonary arterial compliance as a sensitive indicator of the effects of early increase in PAWP and mainstay marker of prognosis in either heart failure with reduced ejection fraction (HFrEF)[8,9] or heart failure with preserved ejection fraction (HFpEF).[10]

Despite the multiple efforts for a reliable definition, Group 2 PH is often identified and merely diagnosed by echocardiography, whereas mPAP is typically not calculated and, instead, pulmonary artery systolic pressure (PASP) is estimated from tricuspid regurgitation Doppler velocity added to an estimate of right atrial pressure. In this situation, a PASP of 35 to 45 mm Hg is typically considered mildly elevated, whereas 46 to 60 mm Hg and greater than 60 mm Hg are considered even if not definitive yet moderately elevated and severely elevated, respectively.[11–13] This approach, offers the advantage to screen large subsets of patients, advancing the suspicion of PH and promoting further investigational steps.

Overall, consistency and uniformity in left-sided PH hemodynamic definition and identification of the most appropriate parameters for staging Group 2 is still under scrutiny.[3]

EPIDEMIOLOGY

Prevalence of Group 2 PH varies depending on the population studied, the methods (echocardiography or RHC) and the hemodynamic criteria (Venice or ESC/ERS Guidelines) used to diagnose and stage PH. Overall, it seems to approximate 60% of cases of HF and, in a large number of cases, a sustained elevation in pulmonary pressures is accompanied by right ventricular dysfunction and uncoupling with the pulmonary circulation.[14,15] In patients with acute decompensated HF, PH is diagnosed in a different rate, ranging from 25% to 75% of cases.[16,17]

Interestingly, PH seems to occur even more frequently in HFpEF and its development of PH does not directly correlate with the degree of left ventricular (LV) ejection fraction (EF) reduction.[18] In 3 studies of patients with HFpEF, PH was present in 36%, 52%, and 83%.[19–21] Recent analysis performed in 387 patients with HFpEF evaluated by RHC, the prevalence of PH was 75%.[22]

How frequent are the Ipc-PH and Cpc-PH phenotypes? Again, it depends on Cpc-PH definition, even though it is now clear that the condition of DPG greater than 7 mm Hg with a PVR less than 3 WU account for a very small portion of patients[7] and definition of Cpc-PH across centers should be exclusively based on PVR.

In the case series by Gerges and colleagues[23] performed in a large retrospective and prospective cohort of patients with either HFpEF and HFrEF showed that Cpc-PH, calculated by DPG criteria, was detectable in 20% of cases. In HFrEF and Cpc-PH, associated risk factors were chronic obstructive pulmonary disease and lower right ventricular to pulmonary circulation coupling, as assessed by the ratio of transtricuspid annular peak systolic excursion (TAPSE)/PASP, while in young age valvular heart disease and TAPSE/PASP were associated with HFpEF.

In 102 consecutive patients with HFpEF, Cpc-PH, calculated by PVR or DPG, was diagnosed in 31% and presented with a higher incidence of diabetes, lower functional capacity, and higher rates of HF hospitalization.[24] In a larger population with HFrEF, the pooled rate of Cpc-PH, based on ESC Guidelines criteria, was approximately 60%.[7]

PATHOPHYSIOLOGY AND CLINICAL CORRELATES

The primary driver of the postcapillary process in PH due to left heart disease is an elevated LAP, estimated by PAWP, even though there may be lack of correspondence in some cases,[25] which is transmitted backward to the pulmonary venous system, pulmonary capillaries, and arteries, and ultimately to the right ventricle. This hemodynamic cascade is the key to better understand and target Group 2 PH.

Fig. 1 depicts the hemodynamic determinants of mPAP changes. Overall, the pulmonary and systemic circulations have important hemodynamic and anatomic differences. Vascular