

REVIEW

Reactive pulmonary hypertension in left heart disease “Post-capillary PH with a pre-capillary component”

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Abstract: Pulmonary hypertension (PH) due to left heart disease (LHD) is the most common form of PH seen in clinical practice, being a marker of disease severity and worse prognosis. An important subgroup of these patients present with significant PH not explained by a passive increase in left-sided filling pressures, also known as “out of proportion” PH. Patients with “out of proportion” PH have a pulmonary arterial component to the PH resulting in a mixed picture of pre-capillary and post-capillary PH. These changes determine an increased transpulmonary gradient (TPG) and a disproportionate increase in the pulmonary pressure compared to the level of capillary wedge pressure. Factors leading to reactive PH are still poorly understood. Also, the optimal therapeutic approach of these patients remains unknown. Better knowledge of the pulmonary vascular structure and function perturbations that cause reactive PH is crucial in order to improve prognosis. In this review we discuss the current available literature and novel treatment strategies for this condition.

Keywords: pulmonary hypertension, reactive, heart failure, prognosis, treatment, left heart disease

Rezumat: Hipertensiunea pulmonară (HTP) asociată bolilor cordului stâng (BCS) este cea mai frecventă formă de HTP, fiind un marker de severitate a bolii și de prognostic negativ. Un subgrup important de pacienți prezintă HTP semnificativă ce nu poate fi explicată numai printr-o creștere pasivă a presiunilor de umplere ale cordului stâng, forma de HTP numită și HTP “disproporționată”. Pacienții cu HTP “disproporționată” prezintă o componentă arterială pulmonară rezultând într-o imagine mixtă de HTP precapilară și postcapilară, reflectată de o creștere a gradientului transpulmonar (GTP) și a rezistenței vasculare pulmonare (PVR). Termenul HTP reactivă sau “disproporționată” a fost utilizat pentru a identifica această populație, deoarece severitatea HTP este “disproporționată” creșterii presiunii venoase pulmonare. Factorii care duc la dezvoltarea HTP reactivă nu sunt clari. Mai mult, strategia terapeutică optimală la acești pacienți rămâne neclară. Înțelegerea mai bună a perturbărilor în structura și funcția vasculară pulmonară care determină această formă de HTP este esențială pentru a îmbunătăți prognosticul. În acest review discutăm datele actuale de literatură precum și noile strategii de tratament pentru această afecțiune.

Cuvinte cheie: hipertensiune pulmonară, reactiv, insuficiență cardiacă, prognostic, tratament, bolile cordului stâng

INTRODUCTION

Left heart diseases (LHDs) are the most frequent cause of pulmonary hypertension (PH). LHDs determine an increase in left ventricular filling pressures and pulmonary venous pressures¹.

Presence of PH in patients with LHD and heart failure is associated with a decrease in exercise tolerance, worsening of dyspnea and increased mortality, independently from the underlying cause²⁻⁶.

PH due to LHD is defined as combination of both elevated mPAP (≥ 25 mmHg) and elevated capillary wedge pressure PCWP (>15 mmHg). PH secondary to LHD is classified in Group two of PH in the most recent classification of PH and includes three etiologies: left heart systolic dysfunction, left heart diastolic dysfunction, and left valvular disease⁷.

An important group of patients with LHDs have a disposition to develop a pre-capillary component to the increased pulmonary pressure, resulting in a mixed picture of pre-capillary and post-capillary PH⁷. These patients present with a reactive or “out of proportion” PH defined as elevated pulmonary vascular resistance (PVR ≥ 3 Wood units) and increased transpulmonary gradient (TPG ≥ 12 mmHg), where the TPG is the difference between mean pulmonary pressure and left atrial pressure. Another term used to define this clinical entity is “mixed PH” as to emphasize both pre-capillary and post-capillary contributions to the elevated pulmonary arterial pressure (PAP)⁸.

Definitions and Terminology

Based on the TPG and PVR values, there are two major distinct categories of PH due to LHD: Passive and Reactive PH (Table 1).

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Passive Group 2 PH is defined by normal TPG and PVR with elevated mPAP values corresponding to the PCWP values. This type of PH represents the form with the highest prevalence and is seen most often in the early stages of HF. There are no significant associated abnormalities in the pulmonary artery structure or function, therefore specific pulmonary artery vasodilator therapy is not considered.

Reactive Group 2 PH is defined by an elevated TPG ≥ 12 mmHg and PVR ≥ 3 Wood units, indicating the presence of functional and/or structural abnormalities of the pulmonary arterial vasculature besides the elevated PCWP. The mPAP values are disproportionately increased compared to the PCWP.

Reactive PH is further classified into reversible or irreversible PH, depending on the response of TPG and PVR to pharmacological interventions.

Reactive reversible Group 2 PH is defined by normalization of the TPG and PVR during vasodilator challenge, suggesting a predominance of functional over structural abnormalities of the pulmonary arterial vessels. This type of PH may represent the transition from passive to reactive PH⁹.

Reactive irreversible Group 2 PH is defined by a PVR which can not be reduced to < 3 WU after alleviation of the high downstream pressure. Structural over functional abnormalities of the pulmonary arterial vascular bed are presumed to exist. Histological changes of pulmonary vasculature bed appear to be the same as in precapillary forms of PH¹⁰. Thus, this group may be considered as a target for therapy with a specific pulmonary artery vasodilator agent.

Epidemiology

PH due to LHD has a highly variable prevalence. Although it represents the most common form of PH, there

are less epidemiological data for this group compared to other forms of PH¹¹. Different studies have shown that PH is present in 68% to 78% of patients with heart failure with reduced ejection fraction (HFrEF) being associated with an increased morbidity and mortality¹²⁻¹⁴. In a recent study, 80% to 90% of patients with HF had PH, and over half had reactive PH regardless of left ventricle ejection fraction¹⁵. More recent data suggest that the prevalence of reactive PH is similar in all ejection fraction groups of patients with LHD. Ghio et al, reported reactive PH in $> 60\%$ of their patients with moderate or severe HF¹⁶. Other studies reported an incidence of reactive PH in symptomatic HFrEF of 36% to 47%^{8,17}. Furthermore, as the severity of HF increases, reactive PH is more likely to be present⁸. In a series of 242 patients with acute decompensated heart failure, reactive PH was present in 40% of patients¹⁸. Similarly, reactive PH was present in 41% to 50% of a pretransplant HF population^{19,20}.

In left sided valvular diseases, the prevalence of PH increases with the severity of the defect and of the symptoms. Wood observed severe precapillary PH (PVR ≥ 6 WU) in 26% of 300 patients with mitral stenosis²¹. According to a recent study, PH can be found in virtually all patients with severe symptomatic mitral valve disease and over half of them present reactive PH²². Another study showed that 65% of patients with symptomatic aortic stenosis present PH and almost one third of them reactive PH²³.

Furthermore, it appears that women are more prone to reactive PH, suggesting that hormonal and autoimmune pathways may be implicated in this pathology²⁴.

Pathophysiology

In all patients with LHD the primary event leading to PH is a passive backward transmission of filling pressures, mostly caused by left ventricular diastolic dysfunction¹⁰. Several studies suggest that venous congestion might trigger pulmonary vasoconstriction and vascular remodeling in this PH population^{25,26}.

Pulmonary vasoconstriction in PH due to LHD is caused by endothelial dysfunction, primarily as a consequence of the imbalances between nitric oxide (NO) and endothelin 1 (ET1) signaling^{27,28}. Nitric oxide is important in regulating pulmonary vascular tone in patients with HF and PH. It has been shown that infusions of NG-mono-methyl-L-arginine, an inhibitor of NO production, results in a lower degree of dose dependent vasoconstriction in heart failure patients with reactive PH compared with those with passive PH or

Table 1. Classification of PH due to LHD (Group 2)

Nomenclature	Description	Physiologic definition	Hemodynamic criteria
1. Passive PH	Group 2 with elevated left cardiac filling pressure	Post-capillary (passive congestion) PH	Mean PAP ≥ 25 mmHg, PCWP ≥ 12 mmHg, TPG ≤ 12 mmHg or PVR ≤ 3.0 WU
2. Reactive PH	Group 2 PH with elevated left ventricular cardiac pressure and increased PVR	Pre- and post-capillary pulmonary hypertension	TPG ≥ 12 mmHg or PVR ≥ 3.0 WU
2.1 Reactive reversible PH	Responsive to pharmacologic (vasodilators and/or inodilators)		TPG ≤ 12 mmHg or PVR ≤ 3.0 WU
2.2 Reactive irreversible PH	Not responsive to pharmacologic		TPG ≥ 12 mmHg or PVR ≥ 3.0 WU

healthy individuals²⁷. ET1, a peptide with vasoconstrictor and platelet aggregating actions, is widely dispersed in the pulmonary endothelium and abundant in the pulmonary vascular endothelial cells in patients with PH due to LHD²⁸⁻³⁰.

Pulmonary vascular remodeling is initiated by local activation of growth stimuli, such as angiotensin II, endothelin 1 and hypoxia³¹. ET1, apart from its vasoconstriction effect, causes proliferation and hypertrophy of vascular smooth muscle cells and increases collagen synthesis²⁹. Muscularization of the acinar arterioles is determined by fibroproliferative changes of the myofibroblasts derived from the arterial media. It has been shown that in patients with advanced HF awaiting heart transplantation, the pathological changes seen in small and medium pulmonary arteries lead to pulmonary vascular disease, increased right ventricle (RV) afterload, and RV failure³².

Transition from passive to reactive PH is highly variable in LHD patients and does not appear to be consistently related to the severity of PWC elevation^{10,13}. In this context, it was suggested that a genetic component plays a role in the pathophysiology of these patients. Thus, a reduced expression of bone morphogenetic protein receptor, coupled with increased expression of angiotensin-1, was found in various forms of PH, including PH secondary to mitral valve diseases, suggesting a common pathway in disease progression³³. However, the genetic substrate responsible for the remodeling processes within individual patients with PH secondary to LHD remains poorly understood.

Clinical profile

The clinical profile of patients with PH due to LHD does not usually help in differentiating the reactive from the passive forms of HP. However, patients with reactive PH may present with signs and symptoms that are generally not found in other forms of PH such as orthopnoea and paroxysmal nocturnal dyspnoea¹¹. Their chest radiographs may show additional pulmonary vascular congestion, pleural effusion, and left ventricle hypertrophy may be evident on electrocardiogram.

The clinical distinction between PH due to HF with preserved ejection fraction (PH - HfpEF) and pulmonary arterial hypertension (PAH) is important because often these two groups of patients share similar hemodynamic profile but very distinct therapeutic strategies. Compared with patients with PAH, patients with reactive PH - HFpEF are older and have a higher prevalence of cardiovascular comorbidities. They had worse exercise capacity and renal function and more

frequently left atrial enlargement. Also, PH is less severe in PH - HFpEF patients than in PAH patients and they have higher cardiac output³⁴.

Diagnosis and important hemodynamic concerns

PH due to LHD is defined as combination of both elevated mPAP (≥ 25 mmHg) and elevated capillary wedge pressure PCWP (>15 mmHg)⁷. Although echocardiography may be a useful screening tool, invasive measures of PCWP, TPG and PVR by RHC may be needed in order to confirm a diagnosis of reactive PH due to LHD.

The PVR and TPG are commonly used in clinical practice but with the disadvantage of representing a composite variable, with an interdependent numerator and denominator (changes in flow influence pressure in the pulmonary circulation). Therefore, they are highly sensitive to changes in both flow and filling pressures but do not reflect changes in the pulmonary circulation at rest^{35,36}. In contrast, diastolic PAP when compared with systolic pulmonary artery pressure and mPAP is less influenced by PAWP, which might be explained by a lower sensitivity to vessel distensibility³⁵. In normal subjects, diastolic pulmonary artery gradient (DPD) lies in the 1-mmHg to 3-mmHg range, and in patients evaluated for cardiac disease the DPD remains ≤ 5 mmHg in 94% of the cases^{37,38}. This suggests that, when PH develops in heart diseases, DPD increases >5 mmHg in one-half of the cases and that the increase in diastolic PAP is somehow unrelated to the changes in PAWP. Therefore, the DPD might be seen as a potential marker of changes in the pulmonary circulation. Although based on a strong pathophysiological reasoning, the respective value of the DPD should be further explored, including its role in predicting outcome³⁸.

Treatment

There is no specific treatment for PH due to LHD. The basic treatment of this pathology is the management of the underlying cardiac disease^{8,15}.

In PH due to LHD, the reduction in pulmonary pressure by LHD suitable therapy is mainly due to wedge pressure reduction and it occurred in all patients, suggesting that a passive element is also present in patients with reactive PH³⁹. However, for patients with reactive PH, the reduction in PWCP does not lead to a normalization of the TPG and mPAP, suggesting that other therapeutic strategies, aimed at the arterial pulmonary vasculature, might be useful in these patients^{40,41}.

In candidates for heart transplantation with reactive forms of PH not responding to vasodilatory treatment,

left ventricular assist device (LVAD) improved pulmonary hemodynamics. Moreover, the significant reduction of the PVR secondary to LVAD use improved the operability of these patients and was associated with good post transplantation outcomes⁴²⁻⁴⁶.

Although no definite evidence is available for supporting the use of PAH therapies in PH associated to LHD, the hemodynamic status of the reactive forms of PH suggests a role for specific vasodilator therapies.

Several trials have tested PAH approved therapies in PH-LHD patients: bosentan^{47,48}, epoprostenol⁴⁹ or darusentan^{50,51}, all showing clinical and hemodynamic negative results. However, none of the studies stratified patients for the type of PH, passive or reactive, although some reported on invasive hemodynamic status.

Given the important role of ET-1 in the pathophysiology of reactive PH, ET antagonists may be effective for ameliorating PH and reversing pulmonary vascular remodeling. In heart transplantation candidates, acute administration of sildenafil prompted a greater improvement in PVR, exercise tolerance and hemodynamics before the transplantation⁵²⁻⁵⁸. Comparable results in exercise tolerance were continuous up to six months with sildenafil in another study⁵⁹. However, the interpretation of these results must be made with great caution, as higher doses of sildenafil than those used to treat PAH were used and there were single center studies.

PAH therapies might be harmful in patients with HFpEF as vasodilator exposure in these patients can lead to a decreased stroke volume⁶⁰. However, in a recent study performed in this PH-population, sildenafil improved clinical and hemodynamic status after six months, with sustained beneficial effects up to one year^{61,62}.

Prognosis

The type of PH is a pivotal determinant of outcome in LHD patients. Survival of these patients is negatively related to the severity of PH and further risk estimation can be increased on the basis of the PH subtype where reactive PH has significant higher risk of death than passive PH¹⁵. Further studies reported that among patients admitted with acutely decompensated HF, six month mortality increased progressively from approximately 8% in no PH to 22% in passive PH and to further 48% in reactive PH¹⁸. Also, it was shown that HF patients with reactive PH and right ventricle (RV) dysfunction have a 2-fold increase in mortality than patients with preserved RV function and comparable LVEF^{16,63,64}. Other studies of heart transplantation can-

didates reported that reactive PH was associated with up to a 3 fold increase in risk of RV failure and early post transplant mortality but if the PVR can be lowered pharmacologically this risk may be reduced^{19,20}.

Summary and future directions

In many patients with LHDs, the degree of PH will be “out of proportion” to the distal PCWP, resulting in a mixed picture of precapillary and postcapillary PH. The outcomes appear to be significantly worse in this case and the optimal therapeutic strategy in these patients remains unknown. The cornerstone of managing PH due to LHD is primary treatment of the LHD but it remains unclear whether PH itself should be a target of therapy. Appropriately powered clinical trials based on pathophysiologic mechanisms will provide an evidence for the efficacy and safety of PH specific therapy, assuming PH due to LHD is a risk factor with a direct deleterious effect rather than simply a marker of outcome.

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