Pulmonary hypertension in left heart disease

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Abstract

Pulmonary hypertension in left heart disease (PH-LHD) is the most prevalent form of PH. It is classified as group 2 PH as per WHO classification. As the prevalence of left heart disease such as congestive heart failure is increasing, the number of patients with associated PH is rising, coupled with high morbidity and mortality. Pulmonary hypertension is initially passive or isolated post-capillary (Ipc-PH) due to increased left sided filling pressures. In long standing cases pre-capillary component is added due to development of pulmonary vascular disease, termed combined post- and pre-capillary PH (Cpc-PH) or reactive PH. We describe the hemodynamics, pathophysiology, role of echocardiography and right heart catheterization in PH-LHD. We discuss the significance of PH associated with congestive heart failure as well as valvular heart disease. Although there is no treatment for PH-LHD, we discuss and critically analyze various studies investigating the role of pulmonary vasodilators in this condition. As PH-LHD is an under studied disease, we highlight the areas where further research is required.

Key words: pulmonary hypertension, left heart disease, congestive heart failure, pre-capillary, post-capillary, pulmonary artery pressure.

Introduction

Pulmonary hypertension (PH) is a severe, progressive disease which may be idiopathic or is associated with or is a sequel of underlying other disease. It is defined as elevation of mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg at cardiac catheterization. A clinical classification characterizes disorders causing PH into five groups, based on similar pathological findings, hemodynamic characteristics, and management (Table I) [1]. Pulmonary hypertension associated with left heart disease (PH-LHD) is classified as group 2 PH and represents the most prevalent form of PH [2].

Typically many patients with left heart disease develop PH as their primary cardiac disorder progresses. Hence the prevalence of PH increases in a particular left heart disease with advancing functional class (Table II) [3–8]. PH-LHD is common in patients with heart failure with preserved (HF-PEF) [4] or reduced ejection fraction (HF-REF) [9] and in valvular heart disease [5–8]. When present, PH-LHD results in more severe
symptoms and worse exercise tolerance [10–13]. In general, the development of PH in a patient with left heart disease portends a poor prognosis vis-a-vis normal pulmonary artery pressures [14].

### Pre-capillary and post-capillary pulmonary hypertension

If the underlying pathology is predominantly in the pulmonary arterioles and small pulmonary arteries, PH is termed pre-capillary. If the underlying cause of raised PAP is left heart disease, PH is termed isolated post-capillary PH (Ipc-PH). By definition, in Ipc-PH the raised PAP is a passive phenomenon meaning there is no intrinsic pathology in pulmonary circulation (at least in the beginning) so as to maintain forward flow in response to elevated left sided filling pressures. However, in many patients chronic passive elevation of PAP leads to pathologic changes in the small pulmonary arteries and arterioles such that the process is no longer passive. The raised PAP in such cases has dual cause: elevated left sided filling pressures and intrinsic pulmonary vascular disease termed combined post-capillary and pre-capillary PH (Cpc-PH).

### Hemodynamics

Pulmonary hypertension is defined hemodynamically by invasive right heart catheterization (RHC) as mPAP ≥ 25 mm Hg and a normal or reduced cardiac output. The severity of PH is graded by Doppler echocardiography based on estimated peak PAP as mild 36–45 mm Hg, moderate 46–60 mm Hg, and severe if > 60 mm Hg. The RHC based grading is by mean PAP: mild 25–40 mm Hg, moderate 41–55 mm Hg, and severe > 55 mm Hg [12, 15–17]. The main hemodynamic parameter that differentiates PH-LHD is pulmonary capillary wedge pressure (PCWP) measured at end-expiration. A PCWP cut-off of 15 mm Hg defines whether PH is pre-capillary (PCWP ≤ 15 mm Hg) or post-capillary (PCWP > 15 mm Hg).

Transpulmonary gradient (TPG) and diastolic pulmonary gradient (DPG) differentiate whether PH is passive or reactive. The TPG is defined as difference between mean PAP and mean PCWP (TPG = mPAP – mPCWP). A TPG < 12 mm Hg defines passive PH and TPG ≥ 12 mm Hg defines reactive PH. Diastolic PAP is less influenced by increased PCWP than systolic PAP and mean PAP. Therefore, raised PCWP will result in marked increase in systolic PAP and mean PAP with or little increase in diastolic PAP [13]. Diastolic pulmonary gradient defined as difference between diastolic pulmonary artery pressure (dPAP) and mean PCWP (DPG = dPAP – mPCWP) is a marker of pulmonary vascular disease. In normal subjects DPG is 1–3 mm Hg.

**Table I. Updated clinical classification of pulmonary hypertension [1]**

| 1 | Pulmonary arterial hypertension |
| 1.1 | Idiopathic PAH |
| 1.2 | Heritable PAH |
| 1.2.1 | BMPR2 |
| 1.2.2 | ALK-1, ENG, SMAD9, CAV1, KCNK3 |
| 1.2.3 | Unknown |
| 1.3 | Drug and toxin induced |
| 1.4 | Associated with: |
| 1.4.1 | Connective tissue disease |
| 1.4.2 | HIV infection |
| 1.4.3 | Portal hypertension |
| 1.4.4 | Congenital heart disease |
| 1.4.5 | Schistosomiasis |
| 1' | Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis |
| 1'' | Persistent pulmonary hypertension of the newborn (PPHN) |
| 2 | Pulmonary hypertension due to left heart disease |
| 2.1 | Left ventricular systolic dysfunction |
| 2.2 | Left ventricular diastolic dysfunction |
| 2.3 | Valvular disease |
| 2.4 | Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3 | Pulmonary hypertension due to lung diseases and/or hypoxia |
| 3.1 | Chronic obstructive pulmonary disease |
| 3.2 | Interstitial lung disease |
| 3.3 | Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3.4 | Sleep-disordered breathing |
| 3.5 | Alveolar hypventilation disorders |
| 3.6 | Chronic exposure to high altitude |
| 3.7 | Developmental lung diseases |
| 4 | Chronic thromboembolic pulmonary hypertension (CTEPH) |
| 5 | Pulmonary hypertension with unclear multifactorial mechanisms |
| 5.1 | Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy |
| 5.2 | Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioliomyomatosis |
| 5.3 | Metabolic disorders: glycogen storage diseases, Gaucher disease, thyroid disorders |
| 5.4 | Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH |

PAH – pulmonary arterial hypertension, BMPR2 – bone morphogenetic protein receptor 2, HIV – human immunodeficiency virus, PH – pulmonary hypertension.
The raised diastolic pulmonary gradient (> 7 mm Hg) in a given patient of PH-LHD suggests setting-in of pre-capillary component (pulmonary vascular pathology) over and above post-capillary component [13]. In one study the patients with TPG > 12 mm Hg who had DPG > 7 mm Hg had worse prognosis [18]. In contrast, another study of 1236 patients with cardiomyopathy and PH-LHD, elevated DPG was not associated with worse survival [19]. Pulmonary vascular resistance (PVR) of ≤ 3 Wood Units (WU) characterizes Ipc-PH, whereas PVR > 3 WU is suggestive of Cpc-PH or reactive PH in the setting of left heart disease (Figure 1). The latest ESC/ERS guidelines recommend combined use of DPG and PVR to differentiate between Ipc-PH and Cpc-PH in PH-LHD [20].

Impact of pulmonary hypertension development on prognosis

The development of PH in left heart disease is a marker of chronicity. Patients with PH-LHD typically have advanced disease and have poorer prognosis [11, 21]. Pulmonary hypertension is associated with increased survival in HF-PEF and HF-REF [4, 9]. In patients with PH-LHD, the right ventricular (RV) function further dichotomizes the risk. The presence of RV dysfunction in patients with PH-LHD is an ominous finding. Ghio et al. have reported RV dysfunction with high mPAP in 57% of their cohort of patients with dilated cardiomyopathy [21]. They found a significant inverse relationship between mPAP and RV ejection fraction. Nonetheless many patients of dilated cardiomyopathy with normal mPAP had RV dysfunction. The presence of RV dysfunction gives prognostic information over and above provided by mPAP [21].

Pre-transplant PH is associated with higher early mortality and poor post-transplant survival. Therefore, assessment of severity of PH is important in determining the candidacy for heart transplantation (HT). In patients with PASP ≥ 50 mm Hg and either TPG ≥ 15 mm Hg or PVR > 3 WU, vasodilator challenge should be administered to see for reversibility of PH. Patients showing reversibility have better prognosis than patients with fixed PH. If initial acute vasodilator challenge is unsuccessful, medical management with diuretics, nitric oxide and inotropes and/or mechanical assist devices may be tried in an attempt to decrease PVR. If PVR fails to decrease by above measures, patient is deemed to have irreversible fixed PH [22]. Severe fixed PH is a contraindication to HT. Oral sildenafil can be tried in patients with irreversible PH associated with heart failure in an attempt to decrease PVR and as a bridge to transplantation. In a study of 18 patients with severe LV dysfunction, sildenafil increased RV ejection fraction from 26 ±7% to 30 ±9%, p = 0.008 and decreased PVR from 5.3 ±1.9 to 3.3 ±1.8 WU, p = 0.01 over a median follow-up of 8.7 months. During follow-up, 5 patients had HT and 6 had LV assist device implantation.

Table II. Prevalence of pulmonary hypertension in left heart disease

| S. No. | Left sided heart disease | Prevalence of PH (%) |
|-------|--------------------------|----------------------|
| 1     | LV systolic dysfunction [3] | 60                   |
| 2.    | LV diastolic dysfunction (PASP > 35 mm Hg) [4] | 83                   |
| 3     | Mitral stenosis (PASP ≥ 50 mm Hg) [5] | 38                   |
| 4     | Mitral regurgitation (PASP > 50 mm Hg) [6] | 23                   |
| 5     | Aortic stenosis (PASP > 50 mm Hg) [7] | 29                   |
| 6     | Aortic regurgitation (PASP ≥ 60 mm Hg) [8] | 16                   |

Note: The above percentages are only approximate values based on the quoted series. It must be emphasized that the occurrence of PH is dependent on severity and duration of left heart disease such that the PH is more common in patients in advanced stages of underlying left heart disease. Further, it is not necessary that all patients with similar severity of particular left heart disease will develop PH or if PH is present it is of equal severity. Nevertheless, the presence and severity of PH signifies poor prognosis. PASP – pulmonary arterial systolic pressure, LV – left ventricular.

Figure 1. Hemodynamic definition of pulmonary hypertension

\[ TPG = mPAP − mPCWP, DPG = dPAP − mPCWP, DPG – diastolic pulmonary gradient, dPAP – diastolic pulmonary artery pressure, TPG – transpulmonary gradient, mPAP – mean pulmonary arterial pressure, mPCWP – mean pulmonary capillary wedge pressure, PH – pulmonary hypertension, PVR – pulmonary vascular resistance, WU – Wood units. \]
tation. All patients showing significant response as evidenced by a decrease in PVR to < 3 WU were alive at follow up compared to non responders who had 44% survival rate [23]. In a comparative study of 15 patients with severe PH receiving oral sildenafil therapy and 104 patients without severe PH who underwent heart transplantation, sildenafil was administered in severe PH group for 163 ±116 days before HT, and 43 ±45 days after HT. Sildenafil therapy resulted in significant decrease in PVR from 5.0 ±1.1 to 3.0 ±1.6 WU, mean TPG decreased from 17.3 ±3.2 to 10.2 ±4.1 mm Hg, and mPAP decreased from 43.9 ±12.5 to 33.4 ±5.8 mm Hg, p < 0.01. As a consequence all severe PH patients could undergo successful HT. Sildenafil could be withdrawn in most patients late after HT. Survival after HT was similar between both the groups [24].

Pulmonary hypertension and RV dysfunction after HT is associated with 3–5 fold increased risk of 30 day mortality. About 10–15% of all HT recipients develop RV dysfunction after transplantation. The addition of oral sildenafil in the post-operative period may allow early withdrawal of inhaled nitric oxide and intravenous drugs administered to reduce PAP [25].

**Persistent/residual pulmonary hypertension in valvular heart disease**

Most patients of valvular heart disease will have significant decrease in PAP after relief of valve stenosis/regurgitation [26, 27]. However, persistent/residual PH is observed in many patients even after successful relief of mitral valve obstruction or regurgitation by percutaneous balloon mitral valvotomy (BMV) or surgical mitral valve replacement [26]. Besides the presence of fixed component of PH, other factors like suboptimal BMV, significant MR after BMV and patient-prosthesis mismatch are responsible for the persistence of PH even after therapeutic intervention [28–30].

In the study by Puri et al. residual PH correlated with functional capacity impairment 7 days after mitral valve replacement as determined by 6 minute walk test [31]. Another study compared 287 patients with persistent PH one year after BMV with 414 patients who did not have PH after BMV. The patients with persistent PH were older, had severe pre-BMV PH, increased Wilkin’s mitral valve echocardiography scores and suboptimal BMV result. Importantly, on long term follow-up persistent PH group had more new onset heart failure and higher need for reintervention [32]. Further patients with atrial fibrillation have increased right atrial dilatation which further increases tricuspid annular dilatation and tricuspid regurgitation [33].

**Pathophysiology of pulmonary hypertension in left heart disease**

The increased pulmonary venous pressure results in disruption of alveolar-capillary walls termed alveolar-capillary stress failure, resulting in capillary leakage and acute alveolar edema [34]. This acute stage is reversible. However with chronically increased pulmonary venous pressure there is irreversible remodeling of the alveolar-capillary membrane as a compensatory mechanism to decrease the frequency and severity of potentially life-threatening pulmonary edema [35].

The remodeling affects both pulmonary venous and arterial system with thickening of the capillary endothelial and alveolar epithelial cell basement membranes and pulmonary veins. These changes reduce the permeability of the alveolar-capillary membrane to fluids, and prevent development of pulmonary edema. The process also results in muscularization of the arterioles and neointima formation along with medial hypertrophy of distal small pulmonary arteries leading to increased pulmonary vascular resistance [36, 37]. Also lymphatic vessels are dilated [35]. With long-standing disease, pulmonary edema becomes less frequent and the clinical picture is dominated by development of PH and right heart failure (Figure 2).

The development of pulmonary vascular disease is variable, with some patients developing severe PH while others being spared of PH despite similar rises in PCWP. While why this happens is unknown, some factors may be responsible. The patients with large compliant left atria may be less prone to development of pulmonary edema and ultimately less severe PH. Also development of AF may make them more prone to develop PH.

**Pulmonary function abnormalities**

The gas diffusion across the alveolar capillary membrane is decreased in HF, the degree of impairment depending on severity of HF [38]. Patients with mitral valve disease have decreased FVC, FEV1 and diffusion capacity of lung for carbon monoxide (DLCO) and increase in residual volume [39]. Structural changes in the alveolar-capillary membrane decrease diffusion capacity of the lung with resultant impedance to gas transfer contributing to exercise intolerance.

**Genetics**

The influence of genetics in development of idiopathic PH (WHO Group 1) is undisputed. Genetic studies have shown that approximately 80% of patients with familial pulmonary arterial hypertension (PAH) and 25% of patients with sporadic PAH carry mutations in the bone morphogenetic protein receptor 2 (BMPR II) [1]. But there are no
studies which have investigated a link between PH-LHD and BMPR II mutations. Endothelin-1 gene polymorphisms have been shown to induce pulmonary hypertension in idiopathic PAH [40, 41]. Although there is no concrete evidence for genetic predisposition, attempt is being made to find predisposing genetic factors in PH-LHD. Serotonin and its transporter protein (5-HTT) have vasoactive and mitogenic properties. Homozygous patients for the long variant of 5-HTT have been shown to be associated with elevated PAP in heart failure [42].

Two-dimensional and Doppler echocardiography

Echocardiography is used for the diagnosis and quantification of severity of left heart disease like valvular heart disease and highlights features suggestive of PH like right atrial (RA) enlargement and RV dilatation, hypertrophy or dysfunction. Echocardiography is a semi-quantitative screening tool for diagnosing PH [43–47]. Doppler echocardiography is used to estimate the right ventricular systolic pressure (RVSP) from tricuspid regurgitation velocity jet by adding estimated RA pressure. The ancillary signs of RV involvement must be present in addition to elevated RVSP to diagnose PH (Table III) [48]. Also peak early diastolic and end diastolic velocities of pulmonary regurgitation (PR) jet continuous wave Doppler trace significantly correlate with mean and end diastolic PAP respectively [49] (Figure 3).

The grading of severity of PH is ideally done by RHC especially when specific pulmonary vasodilator therapy is planned or in the event of diagnostic ambiguity. Although only modest correlation of Doppler derived PA pressures and RHC measured pressures has been reported in earlier studies ($r \approx 0.7$) [50], a recent study of 667 patients undergoing both RHC and transthoracic echocardiography has reported a high correlation of invasive mean PAP and Doppler derived systolic PAP in patients with interpretable TR jets. The degree of correlation decreased in patients who had partially visible TR jet envelope, signifying the importance of TR jet envelope quality in correctly estimating systolic PAP [51]. Echocardiographic features suggesting post-capillary PH include larger left heart...
chambers compared to right heart chambers with LV forming the apex, LV eccentricity index < 1.2 and E/E’ ≥ 10 [52]. The Doppler derived systolic PAP can be monitored periodically non-invasively along with RV assessment by echocardiography.

However, the degree of improvement in RV size, septal position and RV systolic function measured by tricuspid annulus plane systolic excursion (TAPSE), rather than Doppler-estimated PASP in response to PH-specific therapy are predictive of outcomes in Group 1 PH [53]. TAPSE has also been shown to assist in risk stratification in acute pulmonary embolism [54]. Although not specifically studied in PH-LHD, it may be reasonable to follow these patients with regards to above parameters. Other parameters like PA elastance can be calculated by echocardiography which shows moderate correlation with RHC-derived PVR [55].

Table III. Echocardiographic parameters for assessment of right ventricle [43–47]

| Method                                      | Normal range                      | Abnormal value | Remarks                                                                 |
|---------------------------------------------|-----------------------------------|----------------|-------------------------------------------------------------------------|
| Inferior vena cava diameter and inspiratory collapse | ≤ 21 mm, > 50% inspiratory collapse with a sniff suggests normal RA pressure | > 21 mm        | Decreased inspiratory collapse with a sniff < 50% suggests high RA pressure (10–20 mm Hg) |
| Right atrial area (end-systole)             | 14–15 cm²                         | > 18 cm²       | RA enlargement is an indirect measure of RV dysfunction and suggests chronic RA remodeling |
| RV basal diameter                           | 25–41 mm                          | > 41 mm        | Linear dimension of basal RV in 4 chamber view measured in basal one-third of RV inflow at end-diastole |
| RV mid-cavity diameter                      | 19–35 mm                          | > 35 mm        | Transverse RV diameter in middle third of RV inflow                     |
| RV base-to-apex diameter                    | 59–83 mm                          | > 83 mm        | RV foreshortening to be avoided                                         |
| RV/LV basal diameter ratio                  | < 1                               | > 1.1          | Suggests RV dilatation                                                  |
| RV free wall thickness                      | 1–5 mm                            | > 5 mm         | True thickness avoiding trabeculations. Measured from subcostal and parasternal long-axis views |
| Tricuspid annular plane systolic excursion  | 20 ±2.8 mm                        | < 17 mm        | Measure of RV longitudinal function. By M-mode echo directed at lateral tricuspid annulus in 4 chamber view |
| RV fractional area change                   | 47–51%                            | < 35%          | Measured in 4 chamber view as change in RV area from diastole to systole |
| TVI- S’ wave velocity                       | 14–15 cm/s                        | > 9.5 cm/s     | Lateral tricuspid annular systolic tissue velocity                      |
| RV MPI                                      | 0.28 ±0.04                        | > 0.40         | Not limited by RV geometry                                              |
| RVOT acceleration time (AT)                 | > 110 ms                          | > 105 ms and/or midsystolic notching | Inverse relationship between AT and mean PAP |
| Interventricular septum                     | Normally IV septum bows towards RV | Flattening/ bowing of IV septum towards LV | Suggestive of increased RV pressures |
| LV eccentricity index in systole or diastole | 1                                 | > 1.1          | LV antero-posterior to septo-lateral diameters ratio just above papillary muscles in short-axis |
| Early diastolic pulmonary regurgitant velocity | < 1 m/s                          | > 1 m/s        | Estimates mean PAP                                                      |
| Late diastolic pulmonary regurgitant velocity | < 1 m/s                          | > 1 m/s        | Estimates pulmonary artery end-diastolic pressure                       |
| Pulmonary artery diameter                    | –                                 | > 25 mm        | Suggests pulmonary artery dilatation                                     |

IV – interventricular, LV – left ventricle, PAP – pulmonary artery pressure, RA – right atrium, RV – right ventricle, RVOT – right ventricular outflow tract, MPI – myocardial performance index, TVI-S – tricuspid velocity index systolic.
Right heart catheterization

Right heart catheterization is the gold standard for diagnosis of PH and is recommended in patients with PH-LHD [20, 56]. When reliable PCWP cannot be measured on RHC, left heart catheterization is recommended. Right heart catheterization can also assist in ruling out other causes of PH [3, 20]. Exercise testing may be helpful in evaluation of patients with borderline PH associated with left heart disease [56]. Further, fluid challenge with fluid load of 500 ml can unmask underlying LV diastolic dysfunction and occult pulmonary venous hypertension by documenting increased LVEDP to > 15 mm Hg in patients where baseline values were normal [57].

The presence and quantification of PH may explain patient symptoms, affect management decisions and help in assessing prognosis. Resting PAP > 50 mm Hg is Class Ila indication for intervention in asymptomatic severe mitral stenosis (ESC guidelines) [58] and asymptomatic severe mitral regurgitation (MR) (ESC and AHA guidelines) [58, 59]. Exercise induced PH in asymptomatic patients with valvular heart disease and in patients with secondary MR may provide additional prognostic information (Table IV) [60–73].

Management

The management of PH-LHD predominantly involves the treatment of underlying left heart disease. Aggressive medical management of HF-REF primarily includes diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers and mineralocorticoid receptor antagonists [74]. Digoxin can be used as second line drug in patients with persisting symptoms despite being on above mentioned drugs [74]. Corrective valve surgery/percutaneous intervention is recommended and is usually associated with resolution of PH [59]. The recent approval of new drugs for pulmonary artery hypertension has rekindled the interest in the treatment of PH. However the new drugs introduced are for WHO categories Group 1 PH and Group 4 PH. Unfortunately despite being the commonest cause of raised pulmonary artery pressures, PH-LHD remains an under-studied disease with no specific treatment available. Despite promising results in acute hemodynamic studies with some pulmonary vasodilators, the intermediate term results have been disappointing. The reasons for this are many and include: 1) the non-specific selection of patients with systolic and diastolic dysfunction in most studies without adequate segregation based on baseline pulmonary artery pressures except in few studies [75, 76], 2) no studies are available on PH associated with valvular heart disease, an important subset of PH-LHD. At present, there is no evidence that PH specific drug therapy is effective in patients with PH-LHD. Further, the European Society of Cardiology/European Respiratory Society guidelines do not recommend the use of drugs approved for Group 1 PH in PH-LHD due to the lack of evidence [3].

Nitric oxide (NO) and prostacyclin are potent pulmonary vasodilators which improve pulmonary hemodynamics by decreasing pulmonary vascular resistance [77]. The endothelin system is activated in chronic heart failure and elevated plasma ET-1 levels correlate with hemodynamic severity.
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Table IV. Role of exercise in evaluation of valvular disease

| Role of exercise in mitral stenosis | Role of exercise in aortic stenosis | Role of exercise in primary mitral regurgitation (MR) | Role of exercise in secondary mitral regurgitation |
|------------------------------------|------------------------------------|-----------------------------------------------------|--------------------------------------------------|
| • Exercise results in increase in LA pressure, transmirtal mean pressure gradient and systolic PAP [60] | • Severe AS patients with resting elevated PAP (> 50 mm Hg) are often symptomatic and have poor outcome [63, 64] | • Exercise PH (> 60 mm Hg) is frequent (46% patients) in asymptomatic moderate and severe degenerative MR patients and is associated with early development of symptoms [69] | • Although ERO of MR ≥ 20 mm² at rest is a predictor of cardiac death, evaluation of ischemic MR at rest in CHF underestimates the severity of MR and its prognostic implications [72] |
| • Patients with low LA compliance are more symptomatic and show exaggerated increase in PAP with exercise. Sleep E wave downslope is recorded in such patients on continuous wave Doppler trace on mitral valve interrogation resulting in overestimation of calculated valve area by pressure half-time method [61] | • Exercise stress echocardiography is useful in unmasking patients with asymptomatic severe AS who are at high risk of future cardiac events [65] | • Exercise induced increase in MR severity is a strong predictor of exercise PH [69] | • Exercise induced increase in ERO of MR of ≥ 13 mm² and systolic PAP increase of 21 mm Hg are predictors of future CHF hospitalization and cardiac mortality [58, 73] |
| • In asymptomatic patients exercise induced increase in RVSP to > 60 mm Hg should prompt reassessment of symptoms [59] | • Besides poor prognostic markers like increase of mean pressure gradient increase of > 20 mm Hg and lack of contractile reserve on exercise, exercise PH has incremental value in identifying high-risk asymptomatic AS patients [66, 67] | • Exercise PH is an independent predictor of lower event-free survival and need for mitral valve surgery | • The increase in LV filling pressures during exercise in CHF patients is transmitted to the pulmonary vasculature resulting in rise of systolic PAP. Exercise induced increase in MR is associated with increase in pulmonary artery pressure |
| • Increase in systolic PAP ≥ 90% during exercise stress test is associated with development of dyspnea in asymptomatic MS patients and increased need for mitral valve intervention during follow up [62] | • Exercise PH gives additional prognostic information on top of exercise induced increase in aortic trans-valvular gradient | • Pre-operative exercise PH (SPAP > 60 mm Hg) is associated with significantly reduced post operative event free survival including atrial fibrillation, stroke, cardiac-related hospitalization or death [70] | • Exercise induced increase in systolic PAP can occur in secondary |
| | • Exercise stress echocardiography induced PH (systolic PAP > 60 mm Hg) is more common than resting PH in asymptomatic, adversely affecting the prognosis [86, 68] | • Exercise echo is not recommended in asymptomatic patients and in those with reduced LVEF (< 60%) [71] | • MR associated with both LV systolic and diastolic dysfunction [58] |
| | • In asymptomatic severe AS patients exercise stress echocardiography induced PH is a predictor of development of symptoms, occurrence of resting PH and doubling of risk of cardiac events [68] | • Mitral valve surgery is a Class Ib indication in asymptomatic patients with exercise PH ≥ 60 mm Hg (ESC guidelines) [58] | |

AS – aortic stenosis, CHF – chronic congestive heart failure, ERO – effective regurgitant orifice, LA – left atrium, LV – left ventricle, LVEF – left ventricular ejection fraction, MS – mitral stenosis, MR – mitral regurgitation, PAP – pulmonary artery pressure, PH – pulmonary hypertension, RV – right ventricle.

of heart failure and correlate with mortality [78]. Plasma ET-1 acts via two receptor subtypes (ET₁ and ET₂) which leads to pulmonary vasoconstriction, and vascular smooth muscle cell proliferation. In small studies using the dual endothelin-1 receptor antagonist bosentan and tezosentan, and selective endothelin A receptor antagonist darusentan, there was an acute improvement in mean PAP right atrial pressure, PCWP, and cardiac output [78–81]. Intravenous bosentan led to acute improvement in pulmonary hemodynamics in 24 patients with chronic heart failure [78]. In a large placebo-controlled study of patients with acute decompensated heart failure, intravenous tezosentan led to an acute reduction in left ventricular filling pressures, and increased cardiac index but did not result in improvement in dyspnea or pulmonary edema endpoints [78, 82–84]. Further in another large study of 1435 acute HF patients with persistent dyspnea, the dyspnea score, incidence of death and worsening HF was similar between intravenous tezosentan for 24–72 h group and placebo [85]. A number of longer-term studies have not confirmed a benefit for the use of endothelin receptor antagonists in patients with PH associated with HF. However, there was a trend toward reduced HF mortality and morbidity with bosentan [86]. Currently the use of endo-
thein receptor antagonists is not recommended for the treatment of PH associated with left heart disease. It is likely that the patients who have PH disproportionately to their underlying left heart disease will likely benefit from specific PH therapy. However, many of the trials included all patients with congestive heart failure, rather than patients specifically with associated PH. Only few small studies have studied effect of sildenafil in HF patients with PH [87, 88]. Although hypothetically pulmonary vasodilatation may result in increased cardiac filling resulting in increased pulmonary venous congestion, acute hemodynamic study by Lepore et al. showed that PDE-5 inhibition with sildenafil improves cardiac output by balanced pulmonary and systemic vasodilatation [88]. Data from FIRST study suggests that epoprostenol use in systolic heart failure is associated with increased mortality despite decrease in PVR and PCWP and increased cardiac output [89]. Similarly there was increased risk of worsening CHF with endothelin antagonist bosentan in systolic HF initially [86]. However patients who continued treatment for 6 months there was improvement in primary endpoint [86]. Perhaps aggressive diuretic therapy before initiation of pulmonary vasodilator therapy and use of drugs which result in both pulmonary and systemic vasodilatation will be beneficial.

PDE-5 inhibitors such as sildenafil lead to pulmonary vasodilatation and have anti-proliferative action on pulmonary vascular smooth muscle cells. In chronic heart failure, sildenafil acutely lowers PVR and pulmonary arterial pressures, and improves endothelium dependent flow-mediated pulmonary vasodilatation, with a sustained clinical benefit at 6 months [75, 87, 88, 90]. In CHF with PH, sildenafil is associated with increased 6MWT distance, and improved pulmonary hemodynamics at 12 weeks [87, 88]. Longer-term studies have shown that sildenafil is associated with improvement in exercise capacity, cardiac output during and skeletal muscle blood flow during exercise [87]. However, sildenafil in HF-PEF did not result in any significant improvement in exercise capacity or clinical status over 24 weeks [76]. Despite these promising results, the routine use of sildenafil in patients with PH associated with left heart disease cannot be recommended.

Riociguat is a novel soluble guanylate cyclase (sGC) stimulator that sensitizes sGC to endogenous NO and directly stimulates sGC independently of NO, thereby increasing NO by dual means. In addition to causing vasodilatation, it has antifibrotic, anti-proliferative, and anti-inflammatory effects [91]. Although approved for Group 1 and 4 PH, a recent study of 201 patients having PH due to systolic heart failure riociguat did not result in any significant change in mean PAP biomarkers, and CV death or hospitalization versus placebo despite improvement in stroke volume and cardiac index and decrease in pulmonary vascular resistance and systemic vascular resistance [92].

### Conclusions

Pulmonary hypertension is common in patients with left heart disease, and is associated with increased morbidity and mortality. Pathophysiologic mechanisms are complex and comprise of both passive and active components secondary to left atrial hypertension. Echocardiography is screening tool for initial evaluation of patients with PH-LHD. Management of PH focuses upon the treatment of the underlying left heart disease, and associated comorbidities. Although there is no evidence for routine use of PH specific therapies in PH-LHD, there is some suggestion that PDE-5 inhibitors may be useful especially in certain subsets.

### Future directions

At present management of PH-LHD is far from satisfactory. No clear cut guidelines exist as how to manage and follow-up PH-LHD patients. As some patients with similar left heart disease develop PH, while others do not, the factors which predispose to the development of PH need to be elucidated. As genetic predisposition is proven in idiopathic pulmonary arterial hypertension, the role of genetics in PH-LHD needs to be studied. There is a need to better define the echocardiographic markers to differentiate between Ipc-PH and Cpc-PH. As repeated catheterization studies to see the effect of management strategies may be impractical, better echocardiographic prognostic parameters need to be defined. The HF-PEF and HF-REF patients with PH need to be studied separately. Studies of pulmonary vasodilators need to dichotomize patients according to PAP rather than non-specific inclusion of a particular left heart disease. Trials of pulmonary vasodilators in PH associated with valvular heart disease need to be conducted. Future studies targeting lung structural and vascular remodeling in PH rather than only vasodilators will be necessary [93].

### Conflict of interest

The authors declare no conflict of interest.

### References

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62: 34-41.

2. Dupuis J, Guazzi M. Pathophysiology and clinical relevance of pulmonary remodeling in pulmonary hyperten-
sion due to left heart diseases. Can J Cardiol 2015; 31: 416-29.
3. Galie N, Hooper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the 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 the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30: 2493-537.
4. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009; 53: 1119-26.
5. Fawzy ME, Hassan W, Stefadouros M, Moursi M, Shaer FE, Chaudhry MA. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. J Heart Valve Dis 2004; 13: 942-8.
6. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S. Pulmonary hypertension in mitral regurgitation. J Am Heart Assoc 2014; 3: e000748.
7. Malouf JF, Sarano ME, Peillikka PA, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: clinical profile and prognostic implications. J Am Coll Cardiol 2002; 40: 789-95.
8. Khandhar S, Varadarajan R, Turk R, et al. Survival benefit of aortic valve replacement in patients with severe aortic regurgitation and pulmonary hypertension. Ann Thorac Surg 2009; 88: 752-7.
9. Abramson SV, Burke JF, Kelly Jr JI, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992; 116: 888-95.
10. Corte TJ, McDonagh TA, Wort SJ. Pulmonary hypertension in left heart disease: a review. Int J Cardiol 2012; 156: 253-8.
11. 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 Lung Transplant 2012; 31: 913-33.
12. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012; 126: 975-90.
13. Vachiery J, Adir Y, Barberà J, et al. Pulmonary hypertension due to left heart disease. J Am Coll Cardiol 2013; 62: D100-8.
14. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007; 99: 1146-50.
15. Badesch DB, Champion HC, Sanchez MAG, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54: S55-66.
16. Budev MM, Arroliga AC, Jennings CA. Diagnosis and evaluation of pulmonary hypertension. Cleve Clin J Med 2003; 70: S9-17.
17. Fox C, Kalancilik PL, Yarborogh MJ, Jin JY. Perioperative management including non-pharmacological vistas for patients with pulmonary hypertension for noncardiac surgery. Curr Opin Anaesthesiol 2008; 21: 467-72.
18. 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; 143: 758-66.
39. Rhodes KM, Enever K, Nariman S, Gibson GJ. Relation between severity of mitral valve disease and results of routine lung function tests in non-smokers. Thorax 1982; 37: 751-5.

40. Ibrahim E, Kassem A, Zakaria N. The role of the biomarker and the genetic polymorphism of endothelin-1 in pulmonary arterial hypertension among Egyptians. Egyptian J Chest Dis Tuberculosis 2012; 61: 495-500.

41. Calabro P, Limongelli G, Maddaloni V, et al. Analysis of endothelin-1 and endothelin-1 receptor A gene polymorphisms in patients with pulmonary arterial hypertension. Intern Emerg Med 2012; 7: 425-30.

42. Olson TP, Snyder EM, Frantz RP, Turner ST, Johnson BD. Repeat length polymorphism of the serotonin transporter gene influences pulmonary artery pressure in heart failure. Am Heart J 2007; 153: 426-32.

43. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.

44. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-71.

45. Forfia PR, Vachiery J. Echocardiography in pulmonary arterial hypertension. Am J Cardiol 2012; 110 (suppl): 165-245.

46. Bosson E, D’Andrea A, D’Alto M, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr 2013; 26: 1-14.

47. Howard LS, Grapsa J, Dawson D, et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. Eur Respir Rev 2012; 21: 239-48.

48. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation 2001; 104: 2797-802.

49. Masuyama T, Kodama K, Kitabatake A, Sato H, Nanto S, Inoue M. Continuous-wave Doppler echocardiographic detection of pulmonary regeneration and its application to noninvasive estimation of pulmonary artery pressure. Circulation 1986; 74: 484-92.

50. Janda S, Shahidi N, Gin K, Swinston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. Heart 2011; 97: 612-22.

51. Ainsalem M, Sternbach IM, Adigopula S, et al. Addressing the controversy of estimating pulmonary arterial pressure by echocardiography. J Am Soc Echocardiogr 2016; 29: 93-102.

52. D’Alto M, Romeo E, Argiento R, et al. Echocardiographic prediction of pre-versus postcapillary pulmonary hypertension. J Am Soc Echocardiogr 2015; 28: 108-15.

53. Basil A, Liu T, Arkles J, et al. Serial changes in TAPSE correlate with functional assessment and clinical events in patients with PAH. Am J Respir Crit Care Med 2009; 179: A4882.

54. Paczynska M, Sobieraj P, Burzsinski L, et al. Tricuspid annulus plane systolic excursion (TAPSE) has superior predictive value compared to right ventricular to left ventricular ratio in normotensive patients with acute pulmonary embolism. Arch Med Sci 2016; 12: 1008-14.

55. Sinha N, Debahktuni S, Kadambi A, et al. Can echocardiographically estimated pulmonary arterial elastance be a non-invasive predictor of pulmonary vascular resistance? Arch Med Sci 2014; 10: 692-700.

56. Gibbs S. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Thorax 2008; 63 (Suppl I): I-1-41.

57. Fox BD, Shimony A, Langlbreben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. Eur Respir J 2013; 42: 1083-91.

58. Magne J, Pigaro P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular heart disease. A comprehensive review on pathophysiology to therapy from the HAVEC group. JACC Cardiovasc Imaging 2015; 8: 83-99.

59. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: e57-185.

60. Li M, Déry JP, Dumesnil JG, Boudreault JR, Jobin J, Pigaro P. Usefulness of measuring net atrioventricular compliance by Doppler echocardiography in patients with mitral stenosis. Am J Cardiol 2005; 96: 432-5.

61. Schwammenthel E, Vered Z, Agranat O, Kaplinsky E, Rabinoivitz B, Feinberg MS. Impact of atrioventricular compliance on pulmonary artery pressure in mitral stenosis: an exercise echocardiographic study. Circulation 2000; 102: 2378-84.

62. Brochet E, Detaint D, Fondard Q, et al. Early hemodynamic changes versus peak values: what is more useful to predict occurrence of dyspnea during stress echocardiography in patients with asymptomatic mitral stenosis? J Am Soc Echocardiogr 2011; 24: 392-8.

63. Kapoor N, Varadarajan P, Pai RG. Echocardiographic predictors of pulmonary hypertension in patients with severe aortic stenosis. Eur J Echocardiogr 2008; 9: 31-3.

64. Faggiano P, Antonini-Canterin F, Ribichini F, et al. Pulmonary artery hypertension in adult patients with symptomatic valvular aortic stenosis. Am J Cardiol 2000; 85: 204-8.

65. Olaf S, Brala D, Ricarda B, et al. Exercise tolerance in asymptomatic patients with moderate-severe valvular heart disease and preserved ejection fraction. Arch Med Sci 2012; 8: 1018-26.

66. Magne J, Lancellotti P, Pierard LA. Exercise testing in asymptomatic severe aortic stenosis. JACC Cardiol Imag 2014; 7: 188-99.

67. Marechaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J 2010; 31: 1390-7.

68. Lancellotti P, Magne J, Donal E, et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation 2012; 126: 851-9.

69. Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. Circulation 2010; 122: 32-41.

70. Magne J, Donal E, Mahjoub H, et al. Impact of exercise pulmonary hypertension on postoperative outcome in primary mitral regurgitation. Heart 2015; 101: 391-6.

71. Heyning CM, Magne J, Lancellotti P, Pierard LA. The importance of exercise echocardiography for clinical decision making in primary mitral regurgitation. J Cardiovasc Med 2012; 13: 260-5.
72. Lancellotti P, Gerard PL, Pierard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. Eur Heart J 2005; 26: 1528-32.

73. Pierard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. N Engl J Med 2004; 351: 1627-34.

74. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-847.

75. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol 2007; 50: 2136-44.

76. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction. JAMA 2013; 309: 1268-77.

77. Loh E, Stamler JS, Hare JM, Loscalzo J, Colucci WS. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. Circulation 1994; 90: 2780-5.

78. Kiowski W, Sutsch G, Hunziker P, et al. Evidence for endothelin-1-mediated vasoconstriction in severe chronic heart failure. Lancet 1995; 346: 732-6.

79. Torre-Amione G, Young JB, Colucci WS, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2003; 42: 140-7.

80. Louis A, Cleland JGF, Crabbe S, et al. Clinical Trials Update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER and RENAISSANCE and cachexia and cholesterol in heart failure. Highlights of the Scientific Sessions of the American College of Cardiology. 2001. Eur J Heart Fail 2001; 3: 381-7.

81. Spieker LE, Mitrovic V, Nol G, et al. Acute hemodynamic and neurohumoral effects of selective ET-A receptor blockade in patients with congestive heart failure. J Am Coll Cardiol 2000; 35: 1745-52.

82. Coletta AP, Cleland JGF. Clinical trials update: highlights of the scientific sessions of the XXIII Congress of the European Society of Cardiology-WARIS II, ESCAMI, PAFAC, RITZ-1 and TIME. Eur J Heart Fail 2001; 3: 747-50.

83. O’Connor CM, Gattis WA, Adams KF, et al. Tezosentan in patients with acute heart failure and acute coronary syndromes, results of the randomized intravenous tezosentan study (RITZ-4). J Am Coll Cardiol 2003; 41: 1452-7.

84. Kaluski E, Kobi I, Zimlichman R, et al. RITZ-5: Randomized intravenous tezosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema. A prospective, multicenter, double-blind, placebo-controlled study. J Am Coll Cardiol 2003; 41: 204-10.

85. McMurray JJV, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007; 298: 2009-19.

86. Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail 2005; 11: 12-20.

87. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systemic heart failure and secondary pulmonary hypertension. Circulation 2007; 116: 1555-62.

88. Lepore JJ, Maroo A, Bigatello LM, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest 2005; 127: 1647-53.

89. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan international randomized survival trial (FIRST). Am Heart J 1997; 134: 44-54.

90. Guazzi M, Tumminello G, Marco FD, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. J Am Coll Cardiol 2004; 44: 2339-48.

91. Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation 2011; 123: 2263-73.

92. Bonderman D, Ghio S, Felix SB, et al.; the Left ventricular systolic dysfunction associated with Pulmonary Hypertension riociguat Trial (LEPHT) study group. Riociguat for patients with pulmonary hypertension due to systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo controlled, dose-ranging hemodynamic study. Circulation 2013; 128: 502-11.

93. Gurtu V, Michelakis ED. Emerging therapies and future directions in pulmonary arterial hypertension. Can J Cardiol 2015; 31: 489-501.