Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary hypertension due to left heart disease

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Abstract:

Pulmonary hypertension (PH) due to left heart disease is the most common cause of pulmonary hypertension in the western world. It is classified as WHO PH group II. Different pathophysiologic abnormalities may take place in this condition, including pulmonary venous congestion and vascular remodeling. Despite the high prevalence of WHO group 2 PH, the major focus of research on PH over the past decade has been on WHO group 1 pulmonary arterial hypertension (PAH). Few investigators have focused on WHO group 2 PH; consequently, the pathophysiology of this condition remains poorly understood, and no specific therapy is available. Clinical and translational studies in this area are much needed and have the potential to positively affect large numbers of patients.

In this review, we provide a detailed discussion upon the pathophysiology of the disease, the recent updates in classification, and the diagnostic and therapeutic algorithms.

Key words:

Pulmonary hypertension, left heart disease, pulmonary artery wedge pressure, left ventricular end diastolic pressure, Saudi association for pulmonary hypertension guidelines

Pulmonary hypertension (PH) is increasingly recognized as a common and important complication of left heart disease (LHD), particularly in heart failure and valvular heart disease (VHD).[1] Although, the overall prevalence of PH due to LHD is unclear and varies according to the definition and diagnostic methods, WHO Group 2 PH is the most common cause of elevated pulmonary artery pressure (PAP).[2] Historically, mitral valve disease has probably been the best-described cause of PH.[3,4] In the current era, heart failure is recognized as the predominant cause of elevated left-sided filling pressures resulting in PH.[5] Despite the high prevalence of WHO Group 2 PH, the major focus of research on PH over the past decade has been on WHO Group 1 pulmonary arterial hypertension (PAH). Few investigators have focused on WHO Group 2 PH; consequently, the pathophysiology of this condition remains poorly understood, and no specific therapy is available. Clinical and translational studies in this area are much needed and have the potential to positively affect large numbers of patients.

Pathophysiology of Pulmonary Hypertension Due to Left Heart Disease

A spectrum of pathophysiologic changes, ranging from simple pulmonary venous congestion to significant structural and functional abnormalities of the pulmonary vasculature occurs in WHO Group 2 PH. Early on, PH due to LHD occurs when left-sided ventricular or valvular disease produces an increase in left atrial pressure (LAP), which is transmitted passively into the pulmonary vascular tree.[1] Any increase in the LVEDP or PAWP will consequently raise the level of PAP.

If the pulmonary pressure elevation is merely a result of passive backward transmission into the pulmonary circulation, the transpulmonary gradient (TPG), calculated as the difference between mean PAP (mPAP) and PAWP, remains normal at ≤12 mmHg (postcapillary passive PH). The diastolic pulmonary gradient (DPG), calculated as the difference between the diastolic PAP and PAWP, should also remain normal at <7 mmHg (postcapillary passive PH).[6] This situation is referred to as passive PH or pulmonary venous hypertension. In other circumstances, pulmonary venous congestion may be associated with reactive changes of the pulmonary vessels and hence that the elevation of PAP is greater than that of PAWP. This leads to an increase of the TPG to values >12 mmHg and the DPG to values ≥7 mmHg, and also to an increase in pulmonary vascular resistance (PVR) that the elevation of PAP is contributed to in part by precapillary PH.[6]

This group of patients with LHD who have

an elevated TPG, DPG, and PVR are referred to as mixed or disproportionate PH in the literature.[7,8] However, the use of the word mixed precapillary and postcapillary has been proposed recently as the preferred term.

Schwartzenberg *et al*.[9] and Guazzi and Borlaug[10] recently showed that in more than one-half of patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) the PVR is >3 WU or TPG is >15 mmHg. In some cases, mixed PH is reversible (or reactive) with the administration of a systemic vasodilator or diuretic, implicating a pulmonary vasoconstrictive response to the elevation in left-sided pressures. In other cases, the PH is irreversible (or fixed), implicating vascular remodeling in the pathogenesis of this condition.

In reactive postcapillary PH, the elevation of PVR is due to an increase in the vasomotor tone of the pulmonary arteries and/or to fixed, structural, obstructive remodeling of the pulmonary arterial resistance vessels.[7,8] The morphological and pathological changes of the pulmonary vessels in this type of PH are characterized by enlarged and thickened pulmonary veins, dilation of the pulmonary capillaries, interstitial edema, alveolar hemorrhage, and enlarged lymphatic vessels and lymph nodes.[11,12]

The distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis.[11] The functional component of reactive PH is reversible under acute pharmacological testing with pulmonary vasodilators, whereas the structural obstructive changes, characterized mainly by medial hypertrophy and intimal proliferation of the pulmonary arterioles, do not respond to acute vasodilators.[2]

Which factors lead to reactive PH and why some patients develop the acutely reversible or the fixed obstructive components or both remains largely unknown? Pathophysiological mechanisms, however, may include vasoconstrictive reflexes arising from so-called stretch receptors, which are localized in the left atrium and the pulmonary veins.[12]

Finally, patients with WHO Group 2 PH have been shown to have endothelial dysfunction, which favors pulmonary vasoconstriction and proliferation of the vessel wall, is of importance.[11] Chronic elevation of hydrostatic capillary pressures can also result in remodeling with extracellular matrix thickening.[13] Remodeling leads to a persistent reduction in alveolar-capillary membrane conductance and diffusing capacity of the lung.[14] Increases in pressure also result in remodeling, hypertrophy, and fibrous changes at the level of the pulmonary veins and arteries.[15] Furthermore, basal production of the pulmonary vascular vasodilator nitric oxide is relatively deficient, and the sensitivity of the pulmonary vasculature to other cyclic guanosine monophosphate-dependent vasodilators, such as brain natriuretic peptide, may be decreased.[8] In addition, elevated levels of the pulmonary vasoconstrictor endothelin-1 have been demonstrated in patients with elevated left-sided heart pressures.[16] Endothelin-1 causes proliferation and hypertrophy of vascular smooth muscle cells and thus, likely contributes to the pulmonary vascular remodeling seen in patients with PH due to LHD.[8] It should be noted that although endothelin-1 has been implicated in the pathogenesis of WHO Group 2 PH, endothelin receptor antagonists have not been proven to be beneficial in clinical trials.[17,18]

Many factors, such as platelet-derived growth factor, epidermal growth factor, and vascular endothelial growth factor that have been implicated in PAH have not been established in the pathogenesis of PH due to LHD.[19] Persistent elevation of systolic PAP (sPAP) can lead to right ventricular failure from pressure overload. Initially, the right ventricle (RV) becomes hypertrophic in response to high sPAP and can generate much higher pressures than in the normal low afterload state. With time, RV hypertrophy may not be sufficient and the RV dilates, with a subsequent decrease in contractile function and the development of symptoms of right-sided heart failure.[1] It should be taken into consideration that patients with LHD and PH may have an additional precapillary component from another disorder, such as pulmonary embolism or untreated sleep-disordered breathing.

The clinical manifestations of right-sided heart failure, including reduced left ventricular (LV) filling from ventricular interdependence, hepatic and splanchnic congestion, impaired lung lymphatic drainage, and reduced renal sodium excretion, are themselves decompensatory and likely accelerate the clinical deterioration.[10]

Pulmonary Hypertension in Heart Failure

The prevalence of heart failure has been increasing as the population age.[20] The exact proportion of patients with heart failure and PH varies depending on patient subsets, definitions of heart failure and PH, and the method used to estimate PAP. In a cohort of 379 patients with HFrEF, Ghio *et al*. have reported that 236 (62%) had a mPAP >20 mmHg by right heart catheterization (RHC).[21] The prevalence of PH in HFpEF is in the range of 52% (defined as mPAP >25 mmHg by RHC) to 83% (defined as sPAP >35 mmHg by echocardiographic estimates).[22] Regardless of the type of heart failure, PH is an indicator of worse prognosis.[23]

The diagnosis of HFpEF is not always straightforward, and studies have found that it is indeed a major cause of unexplained dyspnea.[24] Distinguishing PH due to HFpEF from PAH may be challenging as both groups of patients often have normal LV ejection fraction and no significant left-sided valvular disease on echocardiogram. Patients with HFpEF may have severe PH with elevated PVR, and this group poses the greatest diagnostic dilemma. The distinction between the two conditions is, however, critical because treatments that are indicated for PAH may be harmful in patients with PH-related to HFpEF.[25-27]

The prevalence of PH in patients with chronic heart failure increases with the extent of clinical severity (modified NYHA classification). Up to 60% of patients with severe systolic heart failure and up to 70% of patients with isolated LV diastolic dysfunction may present with PH.[21] In patients with chronic heart failure, PH is associated with an adverse outcome. In one study, the mortality rate during a 28-month observation period was 57% in patients with moderate PH when compared to 17% in patients without PH.[28] Furthermore, patients with a PVR >6-8 WU have an increased risk of postoperative RV failure after heart transplantation.[11]

Clinical Features

Symptoms of PH are nonspecific, but include dyspnea, fatigue, dizziness, and chest pain. Risk factors that have been associated with PH due to LHD differ from the conditions that are generally associated with PAH and are shown in Table 1. In addition, orthopnea, and paroxysmal nocturnal dyspnea generally are not features of PAH and suggest a primary left-sided heart etiology.

Heart failure with reduced ejection fraction (systolic heart failure)

Heart failure with reduced systolic LV function usually develops as a consequence of ischemic cardiomyopathy (ICM) or dilated cardiomyopathy (DCM). The prevalence of ICM is approximately 3000-4500 cases/million, while DCM occurs at prevalence of approximately 360 cases/million.[23] Observational studies have shown that 60-70% of patients with systolic heart failure develop PH.[21,28] In contrast to PAH, which is an orphan disease, PH associated with left heart failure thus represents a common disease.

In patients with chronic heart failure, there is an inverse correlation between the extent of the increase in both PAWP and PAP and survival.[23] As is the case in PAH, chronic elevation of PAP and/or PVR results in permanent RV strain, which ultimately leads to progressive right heart failure and early death.[21,28] A number of studies have shown that in patients with left heart failure, the presence and extent of PH, the degree of RV dysfunction, and especially the combination of RV dysfunction and PH is associated with a particularly poor prognosis.[29,30] In fact, survival of patients with chronic left heart failure is frequently limited by progressive right ventricular dysfunction.[12]

Heart failure with preserved ejection fraction (diastolic heart failure)

No reliable data on the frequency of LV diastolic dysfunction is available, and the information depends on the definition chosen, the population studied, and the applied diagnostic tool. However, recent studies have consistently shown that, according to echocardiographic criteria, the prevalence of diastolic heart failure is up to 25% of the (elderly) population.[29,30] Comparative studies revealed that the prevalence of HFpEF is greater than that of HFrEF, while the prognostic impact is comparable. The reported 5-year survival rate was 43% in patients with HFpEF when compared to 46% in patients with HFrEF, indicating that the ejection fraction has no significant influence on survival in patients with clinical signs of heart failure.[31] The most common causes for diastolic dysfunction of the left ventricle are hypertensive heart disease and ischemic heart disease (IHD).[12] One population study revealed that PH (defined as sPAP >35 mmHg as assessed by echocardiography) was detected in 83% of patients with diastolic heart failure.[22]

Furthermore, PH was severe in many cases as indicated by a median sPAP of 48 mmHg. Although, the increase in PAP primarily resulted from elevated left-sided filling pressures, it could frequently not be fully explained by pulmonary venous congestion, so that a precapillary component contributed to the extent of PH in many patients. In this study, the correlation between the presence and severity of PH and survival was highly significant (hazard ratio 1.3/10 mmHg pulmonary artery systolic pressure).

Table 1: Causes of PH secondary to LHD

HFrEF; EF ≤50%
DCM
ICM
HFpEF; EF >50%
Hypertensive heart disease
IHD (coronary heart disease)
Diabetic cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Constrictive pericardial diseases
Valvular diseases
Aortic valve stenosis/insufficiency
Mitral valve stenosis/insufficiency
Persistent PH after corrected valve disease
Other causes
Cardiac arrhythmias
Left atrial myxoma/thrombus

HFrEF = Heart failure with reduced ejection fraction, EF = Ejection fraction, HFpEF = Heart failure with preserved ejection fraction, LHD = Left heart disease, PH = Pulmonary hypertension, IHD = Ischemic heart disease, ICM = Ischemic cardiomyopathy, DCM = Dilated cardiomyopathy

Left-sided valvular diseases

In left-sided valvular disease, the prevalence of PH correlates with the severity of the valve disease and clinical symptoms. PH is present in almost all patients with severe, symptomatic mitral valve disease and in up to 65% of patients with symptomatic aortic valve stenosis.[32,33] The prognosis of patients with severe aortic stenosis and PH is dismal.[34] Surgical aortic valve replacement is the recommended treatment for patients with severe aortic stenosis in the appropriate clinical setting. Perioperative complications associated with aortic valve replacement are greater when PH is present preoperatively.[35] However, valve replacement is an effective treatment of the PH associated with this condition and a significant decrease in PAP can be seen immediately after surgery. Some patients will have persistent PH, and these patients were found to have decreased long-term survival.[36] Trans-catheter aortic valve replacement is an emerging therapeutic option, particularly in patients with severe aortic stenosis and PH who are at high risk for surgical valve replacement.[37] PH can also develop in patients with aortic regurgitation. Surgical repair of aortic regurgitation is recommended when symptoms develop or when LV dilation occurs. There does not appear to be an increased risk of mortality or operative complications in patients with aortic regurgitation and severe PH compared with those with mild or no PH, and in most cases, the PAP normalizes with aortic valve replacement.[38]

Mitral valve PH commonly develops in patients with mitral valve disease because of chronically elevated LAP due to either an increased pressure gradient across the stenotic mitral valve or a regurgitant systolic jet. It has been known for >40 years that severe PH can develop in patients with mitral valve disease (sPAP >100 mmHg) with high PVR (>6 WU).[39] This results from a combination of backward transmission of elevated LAP and pulmonary arteriolar vasoconstriction and

remodeling. PVR is reduced dramatically after correction of valvular lesions, and the PVR can continue to fall for months after surgery.[40] The American College of Cardiology/American Heart Association guidelines recommend transcutaneous or surgical intervention in patients with mitral stenosis and PH (sPAP >50 mmHg).[41] The reported operative mortality in patients with PH undergoing mitral valve replacement is highly variable and ranges from 6% to 31%, respectively.[42]

Pulmonary Hypertension and Restrictive Cardiomyopathy

Restrictive cardiomyopathies (as from amyloidosis, sarcoidosis, or prior radiation therapy) should always be considered in the differential diagnosis of patients presenting with elevated left-sided pressures and normal LV systolic function. Although certain echocardiographic findings, including Doppler tissue velocities, may suggest the diagnosis; further testing, including invasive hemodynamics, endomyocardial biopsy, and additional imaging, may be necessary to establish the diagnosis and to differentiate this condition from constrictive pericarditis.[43,44] Restrictive cardiomyopathy is frequently difficult to treat and may result in severe PH, although this phenomenon has not been well studied.[45] Further evaluation and management of these patients is beyond the scope of this review.

Post heart transplant outcome

Increased PVR carries a high risk of both early and late mortality post cardiac transplantation.[46,47] Inability of the transplanted heart to adapt to preexisting significant PH usually results in RV failure. Several studies have addressed the influence of PH in heart transplant patients.

In one study, 410 patients were studied before and after heart transplantation divided into three groups: Group 1 had no PH (PVR <3 WU, TPG <10 mmHg); Group 2 had mild-moderate PH (PVR 3–6 WU, TPG 10–20 mmHg); Group 3 had severe PH (PVR >6 WU, TPG >20 mmHg). Complete reversibility in response to vasodilator and/or inotropic infusion was defined as a drop of PVR <3 WU, while partial reversibility was defined by PVR between 3 and 6 WU. Patients with irreversible PH (PVR >6 WU, unresponsive to vasodilators) were not accepted for orthotopic heart transplantation. PVR and TPG improved significantly in all groups post transplantation at 1 month and 1 year, but there was a significant difference in survival between those with high PVR (>3 WU) compare with those <3WU, (81% vs. 53%) in 5 years.[48]

Diagnostic Work-up

All patients with PH should undergo a complete diagnostic evaluation as those detailed in the International Guideline algorithms. Doppler echocardiography remains the best noninvasive tool in the diagnostic workup of left-sided myocardial damage or valvular disease, and plays a key role in the initial diagnosis of PH.[12] The reliable differentiation between PH owing to LHD and PAH, the measurement of pulmonary hemodynamics prior to valvular surgery, and the preoperative hemodynamic evaluation prior to heart transplantation require RHC.[11] Finally, even in patients with well-diagnosed LHD, other disorders such as pulmonary embolism or lung disease may contribute or might be the primary cause of PH and should be ruled out.

Distinguishing pulmonary hypertension due to heart failure with preserved ejection fraction from pulmonary arterial hypertension

Pulmonary arterial hypertension can be easily differentiated from PH due to HFrEF or VHD based on clinical features and echocardiogram. However, it can be difficult to differentiate PAH from PH due to HFpEF because LV systolic function is preserved in both and because both may have abnormal diastolic parameters. Distinguishing PH due to HFpEF from PAH is vital because the management is dramatically different for the two conditions. PAH-specific therapies may worsen heart failure symptoms and increase hospitalizations when used in patients with PH due to LHD.[17,49] On the other hand, misclassifying and not identifying a patient with PAH in a timely manner will delay treatment that can significantly improve symptoms, exercise tolerance, and survival.[1]

The clinical features and risk factors that may help in distinguishing PAH from PH due to HFpEF are illustrated in Table 2.

Exertional dyspnea and reduced exercise capacity commonly occur in patients with PAH and those with PH due to HFpEF. In both groups, exercise capacity may be limited by an inability to recruit additional pulmonary vasculature or because of failure of pulmonary vascular dilation during exercise, thereby placing an additional load on the RV and preventing the cardiac output from increasing appropriately.[1] Such patients also frequently exhibit a variety of gas exchange abnormalities during cardiopulmonary exercise testing, including an impaired ventilatory efficiency.[50,51] Elevated PAWP and sPAP during exercise may develop in some patients with HFpEF who do not have PH at rest.[52] In patients with HFpEF, diastolic LV dysfunction with increased end-

Table 2: Clinical features distinguishing PAH from PH due to HFpEF

PAH	PH due to HFpEF
Any age	Older age
Association with	Association with
Family history	Systemic hypertension
Drugs (e.g., anorexigens)	Diabetes
CTD	IHD
HIV	Arrhythmia
Portal hypertension	Obesity
Congenital heart disease	High cholesterol
Schistosomiasis	
Dyspnea (exertional) and signs of right heart disease	Dyspnea, orthopnea, PND
ECG	ECG
Right axis and RVH	Left axis and LVH

PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, HFpEF = Heart failure with preserved ejection fraction, CTD = Connective tissue diseases, IHD = Ischemic heart disease, PND = Paroxysmal nocturnal dyspnea, RVH = Right ventricular hypertrophy, LVH = Left ventricular hypertrophy, ECG = Electrocardiography

diastolic stiffness, a steep diastolic pressure-volume relation, and high PAWP at a low workload likely plays a key role in exercise limitation.[53,54] This theory is supported by the finding that diastolic dysfunction is strongly and inversely associated with exercise tolerance.[55]

Investigators have identified certain differences in exercise physiology between patients with PH due to HFpEF and patients with PAH. Importantly, exercise capacity that is more impaired than would be expected from the degree of PH alone is in favour of HFpEF as the main underlying cause, as is an exaggerated hypertensive response to exercise.[56,57]

Patients with PAH have an increase in dead space ventilation because arteriolar obstruction results in decreased perfusion to well-ventilated areas. This manifests as a decrease in end-tidal CO_2 at rest and during exercise.[58] End-tidal CO_2 has been found to be significantly lower in patients with PAH than in patients with PH due to HFpEF and may be used to help differentiate between the two conditions.[59]

Echocardiography

Echocardiographic findings can be used to help separate PAH from PH due to HFpEF, but often are subtle. By definition, both groups of patients have elevated PAP, normal LV function, and no significant VHD. Patients with PH due to HFpEF more often have left atrial enlargement and less often have right atrial enlargement compared with patients with PAH.[56] LV hypertrophy is more suggestive of PH due to HFpEF, whereas right ventricular hypertrophy favors PAH.[60] The use of pulsed-wave Doppler and tissue Doppler to assess filling patterns and diastolic parameters been implicated in the diagnosis of HFpEF and might help in the differentiation of PH due to HFpEF and PAH.[61]

Cardiac catheterization

Right heart catheterization is critical to distinguish between PAH and PH due to LHD in general and HFpEF specifically. Unlike patients with PAH, patients with PH due to LHD generally have elevated left-sided filling pressure. There are, however, many potential pitfalls to keep in mind when using hemodynamics to distinguish between PAH and PH due to LHD. One of the misconceptions is that patients with PH due to LHD will not have an elevated PVR.

Routine hemodynamic assessment is not always adequate, and additional procedures often are needed, particularly when there is a discrepancy between clinical risk factors and hemodynamics and when LV filling pressure is borderline elevated. As distinguishing PH due to HFpEF from PAH relies on a thorough clinical assessment and the accurate interpretation of complex echocardiographic and hemodynamic data, it is recommended that RHC for evaluation of PH be performed in centers with expertise in performing and interpreting RHC data.

Left-sided heart pressures are the most important and most challenging variables to obtain and interpret when distinguishing PAH from PH due to HFpEF. First, PAWP does not always accurately estimate LAP, and a more direct measurement with LVEDP may be needed. Second, critical errors can be made in waveform interpretation. Certain conditions make waveform interpretation more challenging, as when patients exhibit large swings in intrathoracic pressure due to advanced lung disease or obesity or when large V waves are present. Using the digital PAWP read instead of the end-expiration PAWP (when the influence of intrathoracic pressure on intracardiac pressure measurement is least) results in a significant underestimation of LVEDP and thus, misclassification of patients as having PAH rather than PH due to HFpEF.[62] Third, patients with PH due to HFpEF may have a normal resting PAWP and LVEDP after aggressive diuresis. On the other hand, patients with PAH may have slightly elevated PAWP because of the enlarged RV that impinges on the left ventricle and causes increased LV filling pressures (ventricular interdependence).[63] Finally, it is worth emphasizing that long-standing elevation of LV filling pressures can result in arterial remodeling and a significant increase in PVR, as discussed previously.

Additional maneuvers may be used to unmask impaired relaxation of the left ventricle. Provocative maneuvers, including fluid challenge or exercise, can be done during the RHC when the PAWP, LVEDP, or both are normal or mildly elevated (due to pharmacologic unloading, recent diuresis, or both), but there is a high clinical suspicion for pulmonary venous hypertension.

There are no standardized protocols for either of those procedures. However, evidence suggests that administration of 500 ml of isotonic saline over 5-10 min can increase in LV filling pressure (LVEDP or PAWP) significantly and may be helpful in distinguishing PAH from HFpEF.[64]

The results of these tests, however, must be considered with caution and should not be used alone to rule out the diagnosis of PAH.

Figure 1 illustrates the diagnostic strategy for PH due to LHD.

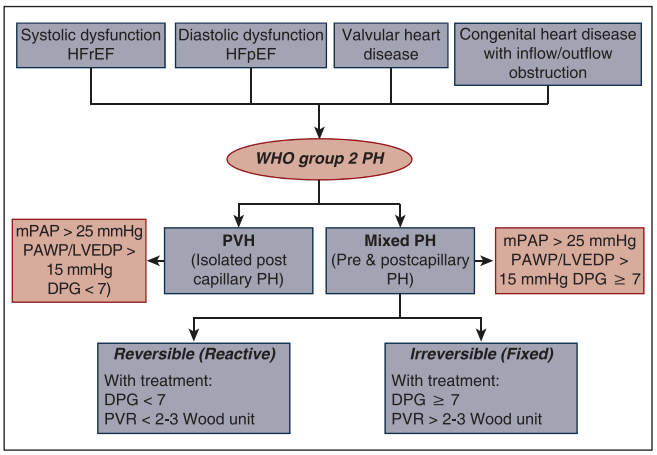

Figure 1: Diagnostic strategy for pulmonary hypertension due to left heart disease. HFrEF = Heart failure with reduced ejection fraction, HFpEF = Heart failure with preserved ejection fraction, PH = Pulmonary hypertension, mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure, LVEDP = Left ventricular end-diastolic pressure, DPG = Diastolic pulmonary gradient, PVH = Pulmonary venous hypertension, PVR = Pulmonary vascular resistance

Treatment

Currently, there is no specific therapy for the treatment of PH due to LHD. A number of drugs (including diuretics, nitrates, hydralazine, angiotensin converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, β-adrenoreceptor blockers, and inotropic agents) or interventions (LV assist device [LVAD], valvular surgery, resynchronization therapy, heart transplantation) for heart failure may lower PAP to a certain extent through a drop in left-sided filling pressures. Therefore, management of PH due to LHD should be aimed at the optimal treatment of the underlying LHD. None of the agents recommended in left heart failure are contraindicated in concomitant PH. Despite the treatment of left heart failure according to guidelines, PH often persists, so that additional treatment options may need to be pursued.

A systemic vasodilator challenge with nitroprusside can be helpful in patients being evaluated for PH due to LHD. Normalization or near normalization of sPAP and PAWP supports the diagnosis of reversible WHO Group 2 PH.[49] The effects of reversibility with nitroprusside on response to medical therapy have not been studied in WHO Group 2 PH. However, reversibility may be predictive of better outcome after heart transplantation.[65] As mentioned, some patients with LHD have an irreversible component to their PH, and the PAP in such patients will not normalize acutely.

Pulmonary Arterial Hypertension-Specific Therapy in Heart Failure

Pulmonary arterial hypertension-specific therapy may cause clinical deterioration and pulmonary edema in patients with elevated left-sided heart pressure. This could hypothetically occur as a consequence of either increased RV output or LV filling from pulmonary vasodilation (decreased RV afterload) or pulmonary venodilation with a consequent increase in capillary pressure that is partly related to an increased V wave.

There are, however, many case reports that have described the use of PAH-specific therapies in patients with PH following surgery.[66-68] Few studies have examined the efficacy and safety of agents that are currently recommended for PAH in patients with left heart failure. Controlled studies evaluating the effects of chronic use of epoprostenol and bosentan in advanced heart failure showed no benefit.[17,66] In case of intravenous epoprostenol, this study was even terminated early, because a higher mortality was documented in the investigational treatment group compared with conventional therapy.[67] As a result, prostacyclin cannot be recommended for patients with HFrEF. Bosentan was also tested in patients with HFrEF. Patients with EF <35% were randomized to receive bosentan or placebo for 26 weeks. Safety concerns, particularly a high incidence of elevated liver function tests, led to the early termination of this trial, and bosentan exhibited no apparent benefit.[67]

In contrast, two trials suggested a role for phosphodiesterase-5 (PDE-5) inhibitors in WHO Group 2 PH. One study of patients with HFrEF and PH showed that sildenafil improved exercise capacity and quality of life.[68] The second trial of 44 patients with HFpEF compared 1 year of sildenafil therapy with placebo. Treatment with sildenafil led to an improvement in pulmonary hemodynamics and RV performance as well as to LV relaxation.[69]

Riociguat, a novel soluble guanylate cyclase stimulator, had recently gained interest as a potential effective therapy in this group of patients. In a recent study, 201 patients with PH due to HFrEF were randomized to double-blind treatment with or riociguat or placebo for 16 weeks.[70]

The primary outcome was the placebo-corrected change in mPAP from baseline at week 16. Although, the decrease in mPAP in the riociguat was not significantly different from placebo (P = 0.10), other hemodynamic parameters, such as cardiac index, stroke volume index, and PVR were significantly improved in the treatment group without changes in heart rate or systemic blood pressure versus placebo. Furthermore, riociguat reduced the Minnesota Living with Heart Failure score (P = 0.0002).

The history of medical therapy for heart failure is full of examples where positive effects of drugs were documented on surrogate endpoints, but eventually turned out to be detrimental and have a negative effect on hard endpoints such as mortality (e.g., PDE type-3 inhibitors).[12] Thus, the use of PAH-specific drugs (including type-5 inhibitors) is not recommended for other forms of PH including PH associated with LHD until robust data from controlled long-term studies are available. It is also unclear if patients with normal or increased DPG would benefit from an additional treatment. As previously mentioned, a sustained reduction of PH can be achieved in weeks to months in most patients successfully operated for mitral valve disease (valve replacement, reconstruction), even if PH represents a risk factor for surgery.[33]

Mechanical support

Mechanical support in PH associated with HFrEF has been another area of study. Consistently, studies have shown that LVAD support reverses fixed or medically unresponsive PH and allows patients with HFrEF and PH to be eligible for orthotopic heart transplantation.[71-74] However, posttransplant survival for patients with HFrEF and PH treated with LVAD does not differ from those patients without PH who receive LVAD.[75]

Conclusion

Pulmonary hypertension due to LHD is the most common type of PH encountered in western countries. Unfortunately, such data is lacking from Saudi Arabia or other countries in the region. The severity ranges from mild to severe disease in which the PVR is commonly significantly elevated as a result of remodeling of the pulmonary vasculature. Distinguishing WHO Group 1 PAH from WHO Group 2 PH may be challenging and should integrate clinical, echocardiographic, and hemodynamic information, ideally in centers with expertise. In patients with slight to moderate LHD, but substantially elevated PAP, PH can dominate the clinical symptoms. In some cases, it may be challenging or even impossible to distinguish the clinical symptoms from PAH.

At this time, the fundamentals of therapy for WHO Group 2 PH are to optimize treatment of underlying conditions.

Table 3: Class of recommendation and level of evidence for treatment of PH due to LHD

Recommendation	Class of recommendation	Level of evidence
Distinguishing WHO Group 1 PAH from WHO Group 2 PH may be challenging and should integrate clinical, echocardiographic and hemodynamic information, ideally in PH expert centres	I	C
In the majority of cases, the pathology and pathophysiology of PH owing to LHD is clearly different from PAH. By lowering left ventricular filling pressure, a significant reduction of the mean PAP and PVR can be achieved in many cases	I	B
The term "out-of-proportion" PH should be abandoned. PH due to LHD should be classified as isolated postcapillary PH (DPG <7 mmHg) or combined postcapillary PH and precapillary PH (DPG ≥7 mmHg)	I	B
The treatment of patients with PH due to LHD should primarily be directed to the underlying LHD	I	A
The general use of targeted PAH drugs outside specific situations and outside the context of clinical trials is strongly discouraged	I	B
In rare and justified exceptions in which a considerable precapillary component is the key aspect of the disease (PAP substantially exceeding the values normally seen in LHDs as manifested by markedly increased DPG or PVR), PAH therapy may be considered. This, however, requires a comprehensive diagnostic workup including right and left heart catheterization; in such exceptional cases, treatment decisions should exclusively be made at expert centers	IIb	C

PH = Pulmonary hypertension, LHD = Left heart disease, PAH = Pulmonary arterial hypertension, PAP = Pulmonary artery pressure, PVR = Pulmonary vascular resistance, DPG = Diastolic pulmonary gradient

Clinical studies on PAH-specific therapies have been disappointing, although small studies suggest that PDE-5 inhibitors may be beneficial. More studies are required and some are currently underway to explore whether a subset of patients, particularly patients with higher pressure and PVR suggestive of pulmonary vascular remodeling, may benefit from therapies that are currently used for WHO Group 1 PAH.

A better understanding of the different phenotypes of PH due to LHD and their respective pathophysiologies is required, so that new therapeutic approaches can be developed.

Table 3 summarizes the class of recommendation/level of evidence for management of PH due to LHD.

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