Pulmonary Hypertension Due to Left Heart Disease—Combine or Not Combined? DPG In or Out? A Practical Approach to the Patient With Suspected Left Heart Disease

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Pulmonary hypertension (PH) due to left heart disease (LHD) is the most common cause of PH in clinical practice. The definition and classification of PH-LHD has evolved in the last 5 years from the 5th World Symposium on PH (WSPH) in 2013 to the most recent 6th WSPH in 2018. Differentiation of PH-LHD, especially PH due to heart failure with preserved ejection from pulmonary arterial hypertension and chronic thromboembolic PH, can be very challenging. Finally, there is unclarity on the role of pulmonary vasodilators in the treatment of PH-LHD. The 6th WSPH consensus proceedings addresses all these topics in a detailed manner. In this article, we review the changes proposed by the 6th WSPH consensus proceedings in the definition, classification, diagnostic evaluation, and treatment of PH-LHD.

INTRODUCTION

Pulmonary hypertension due to left heart disease (PH-LHD), also known as Group 2 pulmonary hypertension (PH), is the most common form of PH in clinical practice.[1] The increase in pulmonary capillary wedge pressure (PCWP) due to LHD initially causes a passive elevation in the mean pulmonary artery pressure (mPAP) that is reversible with a reduction in left-sided filling pressures. The passive increase in mPAP is not associated with precapillary vasoconstriction or remodeling and is referred to as isolated postcapillary PH (IpcPH). However, some patients with IpcPH, over time, develop global pulmonary vascular remodeling including intimal thickening of the precapillary distal pulmonary arteries, arterioles, and the postcapillary venules, commonly referred as combined precapillary and postcapillary PH (CpcPH).[2] Both IpcPH and CpcPH lead to an increase in right ventricular pulsatile and static afterload, ultimately leading to right heart failure and death.[3] Thus, PH-LHD, regardless of the underlying LHD, is associated with increased mortality.[4,5] Compared to IpcPH, CpcPH is associated with worse exercise capacity, reduced survival, different genetic makeup, and closer phenotypic resemblance to PAH.[5,6]

During the most recent 6th World Symposium on PH (WSPH) in 2018, experts in the field of PH-LHD reviewed the literature in the last 5 years and created consensus proceedings that summarized key findings, challenges, and new proposals on how to approach patients with PH-LHD.[7,8] In this article, we review the changes proposed by the 6th WSPH consensus document in the definition, classification, diagnostic evaluation, and treatment of PH-LHD.

DEFINITION OF PH-LHD

The 6th WSPH consensus proceedings have proposed important changes to the definition of PH-LHD. The proceedings define PH-LHD as mPAP > 20 mm Hg with a PCWP > 15 mm Hg.[8,9] Previously, an mPAP ≥ 25 mm Hg was used to define PH.[10] However, multiple recent observational studies show a linear increase in mortality with every 1 mm Hg increase in mPAP from a threshold value of 20 mm Hg.[11,12] Based on this, in the new proposed definition, the threshold value of mPAP to define PH is lowered to >20 mm Hg.[8]

The cutoff value for PCWP to differentiate postcapillary PH from precapillary PH remains at >15 mm Hg, similar to the previous definition. Since accurate measurement of PCWP is key for correct diagnosis of PH-LHD, the consensus proceedings provides multiple tips for proper PCWP measurement.[8] First, PCWP should be measured at mid a-wave in patients with sinus rhythm. In patients with atrial fibrillation, it should be measured at 130–160 milliseconds after the onset of QRS and before the v-wave. The mid a-wave in sinus rhythm and 130–160 milliseconds after the onset of QRS in atrial fibrillation represents end diastole, where PCWP should ideally be measured. Second, the proceedings continue to support the measurement of PCWP at end expiration.[8] Using computer-averaged mean PCWP can underestimate PCWP and lead to misclassification of postcapillary PH as precapillary PH.[13] The end-expiratory PCWP correlates more closely to left ventricular end diastolic pressure than computer-averaged mean PCWP.[14] Third, the document emphasizes the importance of zeroing the transducer properly at the midchest levels with the patient lying supine with legs flat. Fourth, the operator should take 3 PCWP values within 10% variation and average them. Fifth, if there is any question on the accuracy of PCWP, especially when it is higher than the expected value based on the patient's clinical profile, a PCWP saturation should be obtained. A PCWP saturation > 94%

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confirms true PCWP measurement. Alternatively, left ventricular end diastolic pressure should be measured through a left heart catheterization. Finally, the proceedings highlight the importance of a large v-wave. The presence of large v-wave is highly suggestive of underlying LHD, even in the presence of normal PCWP.[8]

CLASSIFICATION OF PH-LHD: CPCPH VERSUS IPCPH

The proceedings document also proposed important changes on how to classify PH-LHD as either IpcPH or CpcPH. The 5th WSPH proposed to use pulmonary vascular resistance (PVR) and diastolic pulmonary gradient (DPG) to classify IpcPH and CpcPH once a diagnosis of PH-LHD is confirmed by a PCWP > 15 mm Hg.[15] To make a diagnosis of CpcPH, one requires the presence of PVR ≥ 3 Wood units or DPG ≥ 7 mm Hg.

However, at the 6th WSPH, CpcPH is defined only based on PVR. CpcPH is defined as mPAP > 20 mm Hg with a PCWP > 15 mm Hg and a PVR ≥ 3 Wood units. DPG has been dropped from the definition.[8] This is based on the literature published in the last 5 years. Several large observational studies and a meta-analysis have documented that many hemodynamic variables predict mortality in patients with PH-LHD including mPAP, PVR, pulmonary arterial compliance, transpulmonary gradient (TPG), and total elastance either alone or in combination.[4,5,16–18] The results are mixed with some studies suggesting one variable being better than the others. Thus, the consensus document acknowledges that the hemodynamic definition of CpcPH is debatable, and there is no single good answer. To overcome the inherent limitations with pure hemodynamic definitions, as it is not always practical to phenotype patients based on a binary value of a single pressure measurement, the document appropriately recommends future studies to evaluate nonhemodynamic diagnostics such as echocardiogram, cardiac magnetic resonance imaging, epidemiology-based risk scores, or biomarkers including genomics, proteomics, and metabolomics to differentiate CpcPH from IpcPH.[8] The ongoing PVDOMICS study sponsored by the National Institutes of Health may hopefully provide some insight.[19]

DIAGNOSTIC EVALUATION OF PH-LHD

The 6th WSPH proceedings recommend a 3-step approach in the diagnostic evaluation of PH-LHD. The purpose of this 3-step approach is mainly to avoid misclassification of PH due to heart failure with preserved ejection fraction (PH-HFpEF) as pulmonary arterial hypertension (PAH). This has significant therapeutic and prognostic implications. None of the currently approved therapies for PAH are effective in PH-HFpEF, and in fact, some are detrimental with increased fluid retention.[20] In addition, this 3-step approach reduces unnecessary overtesting by identifying the right patient population that will benefit from invasive hemodynamic assessment with or without provocative measures.

Step 1: Identify the Clinical Phenotype of the Underlying LHD Associated with PH

The WSPH classification categorizes LHD associated with PH into 3 broad categories: heart failure with reduced left ventricular systolic dysfunction, heart failure with preserved left ventricular systolic function (HFpEF), and left-sided valvular heart disease (aortic and mitral valve disease).[9] PH in the presence of left ventricular systolic dysfunction or moderate to severe left-sided valvular heart disease makes the diagnosis of PH-LHD very straightforward. No further diagnostic evaluation is mandatory.

However, it can be very challenging to differentiate PH-HFpEF from other precapillary forms of PH, especially PAH or chronic thromboembolic disease (CTEPH). PAH and CTEPH patients can have cardiovascular morbidities such as diabetes, hypertension, hyperlipidemia, obesity, atrial fibrillation, and coronary artery disease, similar to PH-HFpEF patients.[21] In addition, PAH and CTEPH patients will have normal left ventricular systolic function, similar to PH-HFpEF patients.[21,22] Finally, PAH and CTEPH patients can have left ventricular diastolic dysfunction similar to PH-HFpEF due to interventricular dependence.[22,23] Thus, to diagnose PH-HFpEF accurately, the proceedings document recommends assessing the pretest probability of PH-LHD, which is the second step in the diagnostic evaluation.[8]

Step 2: Determining the Pretest Probability of PH-LHD

The consensus document categorizes patients into 3 different categories: low probability, intermediate probability, and high probability for PH-LHD based on the combination of 9 different noninvasive variables including age, presence of cardiovascular comorbities, presence of atrial fibrillation, prior cardiac intervention or structural LHD, electrocardiogram, echocardiographic findings, cardiac magnetic resonance imaging, and noninvasive cardiopulmonary exercise testing.[8] Table 1 lists the detailed criteria for each variable for each pretest probability category.

Patients in the low pretest probability category likely have precapillary PH either due to PAH or CTEPH and should undergo further workup for those conditions. Patients in the high pretest probability category probably have PH-LHD, and further evaluations, especially an invasive right heart catheterization, are not necessarily warranted to make the diagnosis, unless they are participating in a clinical trial. However, patients in the intermediate pretest probability category, especially those with abnormal right ventricular size or function, systemic sclerosis, or unexplained dyspnea, should undergo invasive hemodynamic testing with or without provocative measures to determine the exact etiology. This is the third and final step in the diagnostic evaluation of PH-LHD. Of note: this pretest probability categorization is based on prior observational studies and expert consensus but has not been prospectively validated.

Step 3: Invasive Hemodynamic Assessment With or Without Provocative Measures

The proceedings document recommends considering invasive hemodynamic testing in all patients in the intermediate probability group but strongly recommends it in intermediate probability

Table 1. Pretest probability of left heart disease[a]

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidemia, glucose intolerance, or diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention∝	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural left heart disease	Present	No	No
Electrocardiogram	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; $E/e' < 13$
Cardiopulmonary exercise testing	Mildly elevated V'_E/V'_{CO2}; EOV	Elevated V'_E/V'_{CO2}; EOV	High V'_E/V'_{CO2} slope; no EOV
Cardiac magnetic resonance imaging	LA strain or LA/RA > 1		No left heart abnormalities

Abbreviations: LBBB = left bundle branch; LVH = left ventricular hypertrophy; RV = right ventricle; LA = left atrium; EOV = exercise oscillatory ventilation; RA = right atrium; ∝ = coronary artery and/or valvular surgical and/or nonsurgical procedure.

[a]This table is reprinted with permission from Vachiery et al.[8]

patients with systemic sclerosis, right ventricular enlargement or dysfunction, or unexplained dyspnea.[8] These risk factors increase the likelihood of underlying PAH or CTEPH. The consensus document also suggest that the invasive hemodynamic assessments are better performed in PH expert centers because of the technical complexities and nuances involved. The presence of PCWP > 15 mm Hg (properly measured) on invasive hemodynamic assessment confirms the diagnosis of PH-LHD in an intermediate probability patient. In contrast, if the PCWP is between 13 to 15 mm Hg in an intermediate probability patient, PH-HFpEF is still a possibility, and these patients should undergo provocative testing either with exercise or volume challenge to attain the proper diagnosis.

With exercise hemodynamic testing, the proceedings document indicates using the cardiac output (flow) adjusted PCWP rather than using an absolute cutoff value of PCWP to diagnosis PH-LHD. What is an abnormal absolute PCWP during exercise is controversial, and the data are mixed. The consensus document recommends using PCWP/cardiac output > 2 mm Hg/L/min as an abnormal exercise PCWP, as this has been associated with increased serum N-terminal-Pro brain natriuretic peptide levels, reduced exercise capacity, and reduced heart failure free survival.[24]

Due to the complexity involved in exercise hemodynamic testing, the 6th WSPH consensus prefers volume challenge over exercise testing as a provocative measure.[8] PCWP > 18 mm Hg immediately after infusion of 500 mL of saline over 5 minutes is considered as abnormal response and is diagnostic of PH-LHD in patients with intermediate pretest probability.[8]

TREATMENT OF PH-LHD

The main treatment of PH-LHD is proper treatment of the underlying LHD.[10] The 6th WSPH proceedings document recommends strongly against the use of PAH-specific pulmonary vasodilator therapies in patients with PH-LHD. This is based on the lack of large, randomized, controlled trials showing safety and efficacy of pulmonary vasodilator therapies in patients with PH-LHD. In fact, 2 recent trials have reported negative results for pulmonary vasodilator therapies in specific subsets of PH-LHD patients. In the SIOVAC trial, sildenafil 40 mg 3 times a day for 6 months in patients with persistent PH after successful valve replacement or repair procedure at least 1 year before inclusion was associated with worse clinical outcomes.[25] Patients treated with sildenafil had worsening composite clinical score of death, hospital admission for heart failure, change in functional class, and patient global self-assessment.[25] In the Melody trial, macitentan 10 mg once a day for 3 months was associated with increased risk of fluid retention compared to placebo in 63 patients with CpcPH with no significant improvement in PVR, cardiac output, and N-terminal-Pro brain natriuretic peptide levels.[20] The majority of patients in the Melody trial had PH-HFpEF, and all patients had a left ventricular ejection fraction ≥ 30%.[20] Table 2 summarizes the recently completed as well as ongoing clinical trials for treatment of PH-LHD.

WHEN SHOULD WE DO ACUTE VASODILATOR TESTING IN PATIENTS WITH PH-LHD?

There is much uncertainty in clinical practice regarding the utility and clinical significance of acute vasodilator testing in patients with PH-LHD. The only clear indication for acute vasodilatory testing in patients with PH-LHD is in the context of cardiac transplantation in patients with end stage left ventricular systolic dysfunction. There is a linear increase in 30-day post-transplant mortality due to acute right ventricular dysfunction with increase in TPG > 15 mm Hg, PVR > 3 Wood units, and mPAP > 50 mm Hg.[26] Based on this, the current heart transplant guidelines recommend an acute vasodilator challenge if systolic pulmonary artery pressure is ≥50 mm Hg with either TPG ≥ 15 mm Hg or PVR > 3 Wood units and systemic systolic arterial pressure > 85 mm Hg.[27] Intravenous nitroprusside or milirinone are the 2 commonly used agents for acute vasodilatory challenge in patients with PH-LHD being evaluated for heart

Table 2. Clinical trials for PH-LHD[a]

First author or study	Study drug	Dose	Subjects, n	Duration	Population	Primary outcome	Result
Recently completed clinical trials							
Guazzi et al.[28] (NCT01156636)	Sildenafil	50 mg 3 times a day	44	12 months	HFpEF	PVR, RV performance, CPET	Improvement
LEPHT[29] (NCT01065454)	Riociguat	0.5, 1, or 2 mg 3 times a day	201	16 weeks	HFrEF	mPAP versus placebo	No change
Hoendermis[30] (NCT01726049)	Sildenafil	60 mg 3 times a day	52	12 weeks	HFpEF	mPAP versus placebo	No change
SIOVAC[31] (NCT00862043)	Sildenafil	40 mg 3 times a day	231	24 weeks	VHD	Composite clinical score	Worsening in active group
MELODY-1[20] (NCT02070991)	Macitentan	10 mg once daily	48	12 weeks	HF (LVEF > 30%); 75% HFpEF	Safety and tolerability	+10% fluid retention in active group
SOUTHPAW Oral treprostinil (NCT03037580)	Oral treprostinil	Sustained-release oral tablets for 3 times daily administration	310	24 weeks	LVEF ≥50%; RHC within 90 days of randomization; 6MWD > 200 m	Change in 6MWD from baseline to week 24	Stopped early due to low enrollment
Currently ongoing or planned clinical trials							
SERENADE (NCT03153111)	Macitentan	10 mg once daily	300	52 weeks	LVEF ≥ 40% and ESC-defined HFpEF; HF hospitalization within 12 months and/or PCWP or LVEDP > 15 mm Hg within 6 months; elevated NT-proBNP; PVD or RVD	% change from baseline in NT-proBNP at week 24	
SOPRANO (NCT02554903)	Macitentan	10 mg once daily	78	12 weeks	LVAD within 45 days; PH by RHC with PCWP ≤ 18 mm Hg and PVR > 3 WU	PVR ratio of week 12 to baseline	
DYNAMIC (NCT02744339)	Oral riociguat	1.5 mg 3 times a day	114	26 weeks	HFpEF; mPAP > 25 mm Hg and PCWP > 15 mm Hg	Change in CO	
HELP (NCT03541603)	Intravenous Levosimendan	0.075–0.1µg/kg/min for 24 h (weekly)	36	6 weeks	HFpEF; LVEF ≥ 40%; mPAP > 35 mm HG; PCWP ≥ 20 mm Hg, and 6MWD > 50 m	Change from baseline PCWP with bicycle exercise from baseline to week 24	
PASSION (not registered)	Oral tadalafil	40 mg once daily	320	NA	HFpEF; PH with PCWP > 15 mm Hg and mPAP > 25 mm Hg and PVR > 3 WU	Time to first event defined as HF-associated hospitalization (independently adjudicated) or death from any cause	

Abbreviations: HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; PVR = pulmonary vascular resistance; RV = right ventricle; CPET = cardiopulmonary exercising testing; mPAP = mean pulmonary artery pressure; VHD = valvular heart disease; HF = heart failure; LVEF = left ventricular ejection fraction; RHC = right heart catheterization; 6MWD = six-minute walk distance; LVAD = left ventricular assist device; ESC = European Society of Cardiology; NT-proBNP = N-terminal pro brain natriuretic peptide; PVD = pulmonary vascular disease; RVD = right ventricular dysfunction; LVEDP = left ventricular end diastolic pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; RVD = right ventricular dysfunction.

[a]This table is modified with permission from Vachiery et al.[8]

transplant.[27] Intravenous nitroprusside is used if the systemic vascular resistance is elevated, whereas intravenous milirinone is preferred in the presence of normal or low systemic vascular resistance. There is no clear indication for acute vasodilatory challenge with inhaled nitric oxide alone in patients with PH-LHD.

CONCLUSIONS

The proposed definition of PH-LHD has been changed. Mean PAP > 20 mm Hg with a PCWP > 15 mm Hg defines PH-LHD. PVR > 3 Wood units in

the presence of mPAP > 20 mm Hg and PCWP > 15 mm Hg differentiates CpcPH from IpcPH. DPG is no longer needed for the classification of CpcPH. A 3-step approach has been recommended for the diagnostic evaluation of PH-LHD. Careful hemodynamic assessment at expert centers should be considered in patients with intermediate pretest probability for PH-LHD. Treatment of underlying LHD continues to remain the main line of treatment for PH-LHD. Pulmonary vasodilator therapies are strongly not recommended in patients with PH-LHD at this time.

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