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WHO's in Second?

A Practical Review of World Health Organization Group 2 Pulmonary Hypertension

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World Health Organization (WHO) group 2 pulmonary hypertension (PH) due to left-side heart disease (ie, heart failure or left-sided valvular heart disease) is the most common form of PH in western countries. Distinguishing patients with WHO group 2 PH, particularly the subset of patients with PH due to heart failure with preserved ejection fraction (HFpEF), from those with WHO group 1 pulmonary arterial hypertension (PAH) is challenging. Separating the two conditions is of vital importance because treatment strategies differ completely. Furthermore, therapies that are indicated for WHO group 1 PAH may be harmful in patients with WHO group 2 PH. We review the somewhat confusing PH nomenclature and the WHO classification system and rationale behind it. We then focus on left-side heart disorders that cause PH. An aging population and advances in the medical management of common cardiovascular disorders have caused the prevalence of heart failure to rise significantly, with more than one-half of patients having HFpEF. We review contemporary studies that focus on clinical and echocardiographic findings that help to distinguish HFpEF from PAH in the patient with PH. We discuss the typical, and sometimes atypical, hemodynamic profiles that characterize these two groups, review challenges in the interpretation of data obtained by right-sided heart catheterization, and highlight special maneuvers that may be required for accurate diagnosis. Finally, we review the largely disappointing studies on the use of PAH-specific therapies in patients with WHO group 2 PH, including the use of prostacyclins, endothelin receptor antagonists, and the more promising phosphodiesterase-5 inhibitors.

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Abbreviations: E = early mitral flow velocity; E′ = mitral annular tissue Doppler velocity; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAP = left atrial pressure; LHD = left-side heart disease; LV = left ventricular; LVAD = left ventricular assist device; LVEDP = left ventricular end-diastolic pressure; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RV = right ventricle; TPG = transpulmonary gradient; WHO = World Health Organization

Pulmonary hypertension (PH) is more often due to left-side heart disease (LHD) than to pulmonary arterial hypertension (PAH).[1,2] Yet, recognizing this subset of PH, especially in patients with preserved ejection fraction, is challenging. Failing to appreciate the left-side heart basis of PH may result in an unnecessary referral to a PH clinic, the administration of expensive treatments that may do more harm than good, and a delay in treatment of the true primary disease. We discuss how left-sided valvular heart disease and heart failure lead to PH and review their clinical significance. We then focus on the difficulties involved in distinguishing patients with World Health Organization (WHO) group 2 PH from those with WHO group 1 PAH and suggest a practical approach

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to this common problem. Finally, we briefly review prior and current studies examining the effect of PAH-specific therapies on clinical outcomes in patients with WHO group 2 PH.

What Is PH?

PH, defined by a mean pulmonary arterial pressure (PAP) ≥ 25 mm Hg,[3,4] can be a consequence of an intrinsic disorder within the pulmonary arteries, resulting in elevated pulmonary vascular resistance (PVR); an increase in pulmonary venous pressure; an increase in pulmonary blood flow; or a combination of these elements.[5] PH is a clinical and hemodynamic condition that most commonly is a consequence of another illness.

Clinical conditions associated with PH have been classified by the WHO into five major categories since the second World Symposium on PH convened in Evian, France, in 1998.[6] The classification attempts to create categories of PH that have shared pathologic and clinical features as well as therapeutic approaches. The WHO last updated the classification following the 4th World Symposium held at Dana Point in 2008 (Table 1).[7,8] The term "pulmonary hypertension" encompasses all five major categories in the WHO classification. PAH (WHO group 1) comprises idiopathic PH (previously primary PH), hereditary PH, and PH associated with a variety of clinical conditions, as detailed in Table 1. PH associated with LHD (ie, WHO group 2 PH), or postcapillary PH, refers to PH that results from elevated left-sided pressures.

Table 1—*Updated World Health Organization Clinical Classification of PH (Dana Point, 2008)*

Group	Description
1. PAH	Idiopathic (previously primary PH) Heritable (mutations of *BMPR2*, *ALK1*, endoglin, or unknown) Drugs and toxins Associated with connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia
1′ PVOD and/or PCH	
2. PH owing to left heart disease	Systolic or diastolic dysfunction Valvular disease
3. PH owing to lung disease	COPD, ILD, sleep-disordered breathing, high altitude
4. CTEPH	
5. PH with unclear, multifactorial mechanism	Hematologic, systemic, or metabolic disorders

CTEPH = chronic thromboembolic pulmonary hypertension; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PH = pulmonary hypertension; PVOD = pulmonary venoocclusive disease. Adapted with permission from Simonneau et al.[7]

This category was first incorporated into the clinical classification in 1998 and was previously referred to as one of several causes of secondary PH. Other major causes of PH include lung diseases, hypoxia, or both (WHO group 3); chronic thromboembolic PH (WHO group 4); and a variety of hematologic, systemic, or metabolic disorders with unclear or multifactorial mechanisms (WHO group 5). Thorough and methodical evaluation is essential for patients with newly diagnosed PH because prognosis and treatment depend on the underlying cause.

The hemodynamic definition of PH has two major components: mean PAP and the estimated or measured left-sided filling pressure of the heart as reflected by the left ventricular end-diastolic pressure (LVEDP), the left atrial pressure (LAP), or the pulmonary capillary wedge pressure (PCWP). The fourth World Symposium on Pulmonary Hypertension in 2008 recommended that a resting mean PAP ≥ 25 mm Hg, as measured by right-sided heart catheterization, should be considered elevated.[3] This recommendation was based on an extensive review of the existing literature on healthy volunteers, which showed that normal resting mean PAP ranges from 8 to 20 mm Hg.[3,4] The clinical significance of a mean PAP between 21 and 24 mm Hg is unclear. Exercise-induced PH, previously defined as mean PAP > 30 mm Hg during exercise, is a poorly understood entity. A review of right-sided heart catheterization studies found that PAP during exercise depends on exercise level and age and frequently exceeds 30 mm Hg, especially in elderly people.[4] Because of a lack of standardized exercise protocols and uncertainty with regard to the definition of a normal pressure threshold, exercise-induced PH has been removed from the definition.

PH can be further categorized as either precapillary (PCWP or LVEDP ≤ 15 mm Hg) or postcapillary (PCWP or LVEDP > 15 mm Hg) in etiology.[9] WHO group 1 PAH; group 3 PH due to lung disease, hypoxia, or both; group 4 chronic thromboembolic PH; and group 5 PH with an unclear or a multifactorial mechanism all result in precapillary PH and cannot be distinguished on the basis of hemodynamics alone. Early on, PH due to LHD may cause postcapillary PH with elevated left-sided filling pressure and a normal or mildly elevated PVR. However, as will be discussed in more detail later, a significant increase in PVR may subsequently develop in a subset of patients with this condition, which we will refer to as mixed PH.[5,10] Distinguishing precapillary and postcapillary PH on the basis of left-sided filling pressures and PVR can be problematic, and additional maneuvers often are required during right-sided heart catheterization, as discussed later.

The survival of patients with PAH has improved considerably over the past 2 decades, which may reflect

the effects of currently available PAH-specific therapies, a better understanding and closer monitoring of the disease, or differences in the patient population studied. Patients who initiate PAH-specific therapy within 6 months of diagnosis have been found to have 22% to 29% better 7-year survival than the National Institutes of Health registry cohort from the 1980s.[11] However, PAH-specific medications are not indicated for all forms of PH, and identifying the specific cause of PH is necessary for directing therapy to the underlying cause of PH and for selecting appropriate candidates for PAH-specific therapy. Mislabeling a patient with PAH may result in ineffective and costly treatments that often have many side effects.

PH Due to LHD

PH is increasingly recognized as a common and important complication of LHD, particularly in heart failure and valvular heart disease. Indeed, studies have consistently found that the presence of PH in patients with elevated left ventricular (LV) filling pressure predicts worse outcomes and higher mortality.[12,13] Although the overall prevalence of PH due to LHD is unclear and varies according to definition and diagnostic methods, WHO group 2 PH is the most common cause of elevated PAP.[1,2] Historically, mitral valve disease has probably been the best-described cause of PH.[14-16] In the current era, heart failure with preserved ejection fraction (HFpEF) is recognized as the predominant cause of elevated left-sided filling pressures resulting in PH.[17] The estimated prevalence of HFpEF as measured by echocardiography in the general population is 11% to 27%.[18,19] It is worth noting that echocardiographic findings of HFpEF often are subtle and can be missed.

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 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 PH Due to LHD

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. In this review, we use the nomenclature proposed by the International Society for Heart and Lung Transplantation to define different pathophysiologic and hemodynamic forms of WHO group 2 PH (Fig 1).[5] Early on, PH due to LHD occurs when left-sided ventricular or valvular disease produces an increase

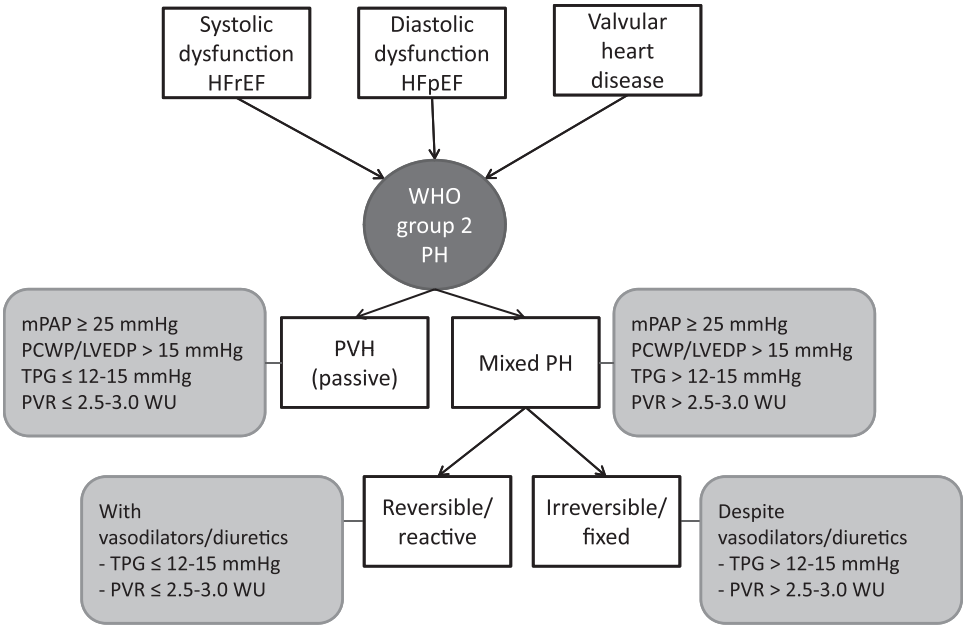

Figure 1. Etiologies and subcategories of WHO group 2 PH. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVH = pulmonary venous hypertension; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient; WHO = World Health Organization; WU = Wood units.

in LAP, which is transmitted passively into the pulmonary vascular tree. Hemodynamically, this results in an elevated PCWP and increased PAP, and in most cases, the transpulmonary gradient (TPG) is normal (< 12-15 mm Hg) and the PVR is not elevated (< 1.5 Wood units).[4] A universal definition of a normal TPG has proven elusive, and, thus, a range is given.[4,7] This situation is referred to herein as passive PH or pulmonary venous hypertension. However, many patients with LHD have long-standing and progressive elevation of left-sided heart pressures, resulting in a PAP that is higher than what would be expected from the elevated LAP alone.[20-22] This group of patients has an elevated TPG and PVR and is referred to as mixed, out of proportion, or disproportionate PH in the literature. In this review, we use the term mixed PH.[5] Schwartzenberg et al[23] and Guazzi and Borlaug[24] recently showed that in more than one-half of patients with heart failure with reduced ejection fraction (HFrEF) and HFpEF the PVR is > 3 Wood units or TPG is > 15 mm Hg. 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 (see later in this article). In other cases, the PH is irreversible (or fixed), implicating vascular remodeling in the pathogenesis of this condition. 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. As with other types of PH, a full diagnostic workup is essential.

Progress has been made in elucidating the pathophysiologic changes that occur in PH due to LHD, although they remain somewhat speculative. High resistance in the pulmonary arteries in patients with PH due to LHD is a result of long-standing elevation of left-sided pressures, dysregulation of vascular smooth muscle vessel tone (reversible), or pulmonary vascular remodeling (irreversible).[5,21,25] Acute elevation of hydrostatic pressure in the pulmonary capillaries causes endothelial and alveolar cell membrane breaks (alveolar capillary stress failure).[25,26] Chronic elevation of hydrostatic capillary pressures can result in remodeling with extracellular matrix thickening.[27,28] Remodeling leads to a persistent reduction in alveolar-capillary membrane conductance and diffusing capacity of lung.[29] Increases in pressure also result in remodeling, hypertrophy, and fibrous changes at the level of the pulmonary veins and arteries.[20,30] Finally, patients with WHO group 2 PH have been shown to have endothelial dysfunction. Basal production of the pulmonary vascular vasodilator nitric oxide is relatively deficient,[21] and the sensitivity of the pulmonary vasculature to other cyclic guanosine monophosphate-dependent vasodilators, such as brain natriuretic peptide, may be decreased.[31] In addition, elevated levels of the pulmonary vasoconstrictor endothelin-1 have been demonstrated in patients with elevated left-sided heart pressures. 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.[21,22] 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.[32-34] Lastly, various factors, like Platelet-derived growth factor, epidermal growth factor, and vascular endothelial growth factor have been implicated in PAH but not established in the pathogenesis of PH due to LHD.[35]

Persistent elevation of PAPs can lead to right ventricular failure from pressure overload. Initially, the right ventricle (RV) becomes hypertrophic in response to high PAPs 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 symptoms of right-sided heart failure. The clinical manifestations of right-sided heart failure, including reduced LV filling from ventricular interdependence, hepatic and splanchnic congestion, impaired lung lymphatic drainage, and reduced renal sodium excretion, are themselves decompensatory and likely accelerate clinical deterioration.[24]

PH in Heart Failure

The prevalence of heart failure has been increasing as the population ages.[36] It is currently estimated that 5.8 million people in the United States have either HFrEF or HFpEF.[36] 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[37] reported that 236 (62%) had a mean PAP > 20 mm Hg by right-sided heart catheterization. The prevalence of PH in HFpEF is in the range of 52% (defined as mean PAP > 25 mm Hg by right-sided heart catheterization)[38] to 83% (defined as pulmonary artery systolic pressure > 35 mm Hg by echocardiographic estimates).[39] Regardless of the type of heart failure, PH is an indicator of worse prognosis.[37,40,41]

The diagnosis of HFpEF is not always straightforward, and studies have found that it is indeed a major cause of unexplained dyspnea.[42,43] As will be discussed later in this review, distinguishing PH due to HFpEF from PAH may be challenging because both groups of patients often have normal LVEF and no significant left-sided valvular disease on echocardiogram.[44] Patients

with HFpEF can have severe PH with elevated PVR, and this group poses the greatest diagnostic dilemma.[45,46] 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.

PH 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[47,48]; 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. Restrictive cardiomyopathy is frequently difficult to treat and may result in severe PH,[49] although this phenomenon has not been well studied. Further evaluation and management of these patients is beyond the scope of this review.

PH in Valvular Heart Disease

Aortic Valve: PH is present in 28% to 56% of patients with severe aortic stenosis, depending on patient selection criteria and definition of PH used.[50] The prognosis of patients with severe aortic stenosis and PH is dismal.[13,51] Surgical aortic valve replacement is the recommended treatment of patients with severe aortic stenosis in the appropriate clinical setting.[52] Perioperative complications associated with aortic valve replacement are greater when PH is present preoperatively.[53] Valve replacement is an effective treatment of the PH associated with this condition, however, and a significant decrease in PAP can be seen immediately after surgery. Some patients will have persistent PH, and these patients have decreased long-term survival.[53] Transcatheter 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.[54]

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 with severe PH compared with those with mild or no PH, and in most cases, the PAP normalizes with aortic valve replacement.[55] Again, there is no current literature to support the use of PAH-specific therapies in patients with aortic regurgitation.

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 (systolic PAP >100 mm Hg) with very high PVR (>6 Wood units).[15,56] This results from a combination of backward transmission of elevated LAP and pulmonary arteriolar vasoconstriction and remodeling.[16,57] PVR is reduced dramatically after correction of valvular lesions,[15,56,58] and the PVR can continue to fall for months after surgery.[59] The American College of Cardiology/American Heart Association guidelines recommend transcutaneous or surgical intervention in patients with mitral stenosis and PH (pulmonary arterial systolic pressure >50 mm Hg).[60] The reported operative mortality in patients with PH undergoing mitral valve replacement is highly variable and ranges from 6% to 31%.[58] PAH-specific therapy can cause clinical deterioration and pulmonary edema in patients with elevated left-sided heart pressure. This could hypothetically occur as a consequence of either increased right ventricular output and LV filling from pulmonary vasodilation (decreased right ventricular afterload) or pulmonary venodilation with a consequent increase in capillary pressure that is partly related to an increased V wave. There are, case reports that have described the use of PAH-specific therapies in patients with PH follow surgery. One report was of a patient with persistent PH following mitral valve repair who experienced improved symptoms and hemodynamics with epoprostenol therapy.[61] The use of sildenafil in a patient with persistent PH following mitral valve replacement has also been reported, and the therapy had a favorable outcome.[62]

Distinguishing PH Due to HFpEF From PAH

PAH can be easily differentiated from PH due to HFrEF or valvular heart disease on the basis of 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.[63] 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.[32,64] 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 probably survival. HFpEF is being increasingly recognized as a major cause of PH, and the diagnostic challenges and implications of separating this entity from PAH have been acknowledged but not extensively studied. Several

epidemiologic studies have started to look at clinical features, echocardiographic findings, and hemodynamic differences that may reliably distinguish the two conditions.

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 HFpEF differ from the conditions that are typically associated with PAH and are shown in Table 2.[38,44,45,65] Additionally, orthopnea and paroxysmal nocturnal dyspnea generally are not features of PAH and suggest a primary left-sided heart etiology.

Simple clinical tests may also be helpful in distinguishing the two etiologies of PH. ECG in advanced PAH typically reveals a right axis deviation, right atrial enlargement, and right ventricular hypertrophy,[67,68] whereas in patients with HFpEF, the typical findings include evidence of left atrial enlargement and LV hypertrophy.[69] The chest radiograph in both scenarios may show enlarged pulmonary arteries[70]; however, pulmonary vascular congestion and pleural effusions generally are not seen in patients with PAH but are found frequently in patients with LHD.[71] Finally, most patients will have a CT scan of the chest at one point or another during the evaluation. Interstitial septal thickening and ground glass changes consistent with chronic pulmonary edema are more consistent with pulmonary vascular hypertension than with PAH. Again, pleural effusions are indicative of a left-sided process.

Echocardiography

Echocardiographic findings can be used to help separate PAH from PH due to HFpEF but often are subtle (Table 3). By definition, both groups of patients have elevated PAP, normal LV function, and no significant valvular heart disease. Patients with PH due to HFpEF more often have left atrial enlargement and less often have right atrial enlargement compared with patients with PAH.[65] LV hypertrophy is more suggestive of PH due to HFpEF,[75] whereas right ventricular hypertrophy favors PAH.[65] Early diastolic mitral annular tissue Doppler velocity (E′) has been shown to correlate with invasive measures of LV relaxation independent of preload.[78] E′ tends to be depressed because of intrinsic left ventricular disease in patients with HFpEF, indicating impaired relaxation.[76] The ratio of early mitral flow velocity (E) to E′ is widely used as a noninvasive measure of LVEDP and LAP.[76,78] Patients with impaired relaxation and elevated LAP have an elevated E but reduced E′, and an E/E′ ratio of >15 is associated with a mean LAP >15 mm Hg.[78] It should be noted that patients with PAH can have impaired LV filling due to left ventricular interaction mediated by the interventricular septum.[63] However, an E/E′ ratio of <8 has been shown to differentiate patients with advanced idiopathic PAH from PH due to heart disease.[76,77] Opotowsky et al[74] recently derived a simple echocardiographic prediction rule to differentiate patients with high PVR as the primary cause of PH from patients with pulmonary venous hypertension. The prediction rule ranged from -2 to $+2$, with a higher score suggesting PH due to pulmonary vascular disease. According to the rule, an E/E′ ratio of >10 and large left atrium each give -1 point, whereas a small left atrial size and right ventricular outflow tract acceleration time <80 milliseconds give $+1$ point. The prediction rule had an area under the curve of 0.921 for PH with high PVR.

Exercise

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

Table 2—*Clinical Features and Risk Factors Distinguishing PAH From PH Due to HFpEF*

PAH[6]	PH Due to HFpEF
Family history	Older age[38,65]
Use of anorexigens, amphetamines	Systemic hypertension[45,65]
Connective tissue disease; systemic sclerosis, SLE, MCTD	Diabetes[45,65]
HIV	Coronary artery disease[45,65]
Liver disease, portal hypertension	Atrial fibrillation[38]
Congenital heart disease	Obesity[38,45,65]
Schistosomiasis	Hyperlipidemia[45]
	Orthopnea, PND
	Exaggerated increase in BP with exercise[66]
ECG: right axis, RAE, RVH[67,68]	ECG: left axis, LAE, LVH[69]

LAE = left atrial enlargement; LVH = left ventricular hypertrophy; MCTD = mixed connective tissue disease; PND = paroxysmal nocturnal dyspnea; RAE = right atrial enlargement; RVH = right ventricular hypertrophy; SLE = systemic lupus erythematosus.

Table 3—*Typical Echocardiographic Findings in PAH and PH Due to HFpEF*

PAH	PH Due to HFpEF
RAE[65,72,73]	LAE[65,74]
RVH[65]	LVH[75]
Flattening and leftward bowing of the interventricular septum[72,73]	
E′ >12 cm/s[76]	E′ ≤ 8 cm/s[76]
E/E′ <8[76,77]	E/E′ >15[74,76,78]

E = early mitral flow velocity; E′ = early mitral annular tissue Doppler velocity; HFpEF = heart failure with preserved ejection fraction. See Table 1 and 2 legends for expansion of other abbreviations.

vascular dilation during exercise, thereby placing an additional load on the RV and preventing the cardiac output from increasing appropriately. Such patients also frequently exhibit a variety of gas exchange abnormalities during cardiopulmonary exercise testing, including an impaired ventilatory efficiency (eg, expired volume per unit time ($\dot{V}E$)/oxygen consumption ($\dot{V}O_2$) ratio of > 34) during exercise.[79,80] Of note, elevated PCWP and PAPs during exercise may develop in some patients with HFpEF who do not have PH at rest.[43] Indeed, in patients with HFpEF, diastolic LV dysfunction with increased end-diastolic stiffness, a steep diastolic pressure-volume relation, and high PCWP at a low workload likely plays a key role in exercise limitation.[81-83] This theory is supported by the finding that diastolic dysfunction is strongly and inversely associated with exercise tolerance.[84,85]

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 favor of HFpEF as the main underlying cause,[65] as is an exaggerated hypertensive response to exercise.[66] Patients with PAH have an increase in dead space ventilation because arteriolar obstruction results in decreased perfusion to well-ventilated areas. This is manifested by decreased end-tidal CO_2 at rest and during exercise.[86] End-tidal CO_2 has been found to be significantly lower in patients with PAH than in patients with PH due to HFpEF and can be used to help differentiate between the two conditions.[87]

Cardiac Catheterization

Right-sided heart catheterization is critical to distinguish between PAH and PH due to HFpEF. Unlike patients with PAH, patients with PH due to HFpEF generally have elevated left-sided filling pressure (PCWP, LVEDP, or both). There are, however, many potential pitfalls to keep in mind when using hemodynamics to distinguish between PAH and PH due to HFpEF (Table 4). 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.

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, PCWP does not always accurately estimate LAP, and a more direct measurement with LVEDP may be needed.[89] 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. A recent study showed that using the digital PCWP read instead of the end-expiration PCWP (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.[90] Large V waves, which are commonly associated with significant mitral regurgitation but may also be seen in patients with high LVEDP,[91] will also drive up the mean PCWP. There is no consensus about how best to calculate the mean PCWP in the setting of large V waves. Third, patients with PH due to HFpEF may have a normal resting PCWP and LVEDP after aggressive diuresis. On the other hand, patients with PAH may have slightly elevated PCWP 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 can be used to unmask impaired relaxation of the left ventricle. Provocative maneuvers, including fluid challenge or exercise, can be done during the right-sided heart catheterization when the PCWP, 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. A typical amount of fluid administered is 500 to 1,000 mL.[88] A significant increase in LV filling pressure (LVEDP or PCWP) during exercise or fluid challenge increases the likelihood of PH due to LHD, although no definition exists on how much increase is pathologic. Finally, a systemic vasodilator challenge with nitroprusside can be helpful in patients being evaluated for PH due to LHD. Normalization or near normalization of PAPs and PCWP supports the diagnosis of reversible WHO group 2 PH. 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.[92,93] It should be noted that some patients with LHD have an irreversible component to their PH, and the PAP in such patients will not normalize acutely. While taking all of the previous discussion into consideration, we recommend that right-sided heart catheterizations for evaluation of PH be performed in expert centers.

Distinguishing PH due to HFpEF from PAH relies on a thorough clinical assessment and the accurate interpretation of complex echocardiographic and hemodynamic data. Thenappan et al[65] examined clinical

Table 4—*Typical Hemodynamics and Pitfalls in Distinguishing PAH From PH Due to HFpEF*

PAH (mPAP > 25 mm Hg)	PH Due to HFpEF (mPAP > 25 mm Hg)	Pitfalls and Additional RHC Maneuvers
Normal PCWP/LVEDP	Elevated PCWP/LVEDP	PAH may have mild elevation in left-sided filling pressures.[63] HFpEF may have normal left-sided filling pressures after aggressive diuresis. Consider fluid or exercise challenge.[88] PCWP may not be an accurate estimate of LAP or LVEDP. Consider direct measurement of LVEDP.[89]
PVR > 2.5-3 WU	PVR ≤ 2.5-3 WU (passive) PVR > 2.5-3 WU (mixed)	It is a misconception that patients with PH due to LHD will not have an elevated PVR.

LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RHC = right-sided heart catheterization; WU = Wood units. See Table 1 and 3 legends for expansion of other abbreviations.

risk factors, echocardiographic findings, and hemodynamics that might distinguish between the two groups. They found that a model incorporating older age, the presence of systemic hypertension and coronary artery disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output best differentiated PH due to HFpEF from PAH, with an impressive area under the receiver operating characteristic curve of 0.97. In this study, the authors used a hemodynamic definition of PH due to HFpEF that consisted of the presence of signs and symptoms of heart failure, an LVEF ≥ 50%, a PCWP or LVEDP > 15 mm Hg, and a PVR > 2.5 Woods units and/or TPG > 12 mm Hg. It should be noted that definitions of PH in HFpEF vary and that no "gold standard" exists. Accordingly, different hemodynamic definitions may yield different results.

Treatment

Currently, the mainstay of treatment of PH due to LHD is to optimize the management of underlying heart failure, valvular disease, or both. For patients with heart failure and clinical evidence of volume overload, this includes consuming a low-sodium diet and using diuretics. Patients with HFrEF should be treated with angiotensin-converting enzyme inhibitors and β-blockers because both have been shown to reduce mortality. Aldosterone antagonists have demonstrated efficacy in HFrEF as well, particularly in patients with severe heart failure and after a myocardial infarction.[94] In patients with HFpEF, management of all contributing conditions, including systemic hypertension, diabetes, obesity, and sleep apnea, is essential. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be considered in patients with HFpEF, especially in those with symptomatic atherosclerosis or diabetes. β-Blockers and calcium channel blockers should be especially considered in patients with hypertension or atrial fibrillation.[94] Detailed discussion of these approaches is beyond the scope of this article. Areas of ongoing investigation include the role of pulmonary vasodilators and mechanical support in the treatment of WHO group 2 PH, and these topics are discussed next.

Pulmonary Vasodilator Therapies

Trials of PAH-specific therapies in heart failure have been largely disappointing (Table 5). Prostacyclins are not recommended for patients with HFrEF because of a clinical trial that was terminated early because of a strong trend toward decreased survival in patients treated with epoprostenol.[64] In addition, epoprostenol therapy was not associated an increase in distance walked or quality of life. Another trial investigated the effects of endothelin receptor antagonists in HFrEF.[32] 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.

In contrast, two trials suggested a role for phosphodiesterase-5 inhibitors in WHO group 2 PH. One study of patients with HFrEF and PH showed that inhibition of phosphodiesterase-5 with sildenafil improved exercise capacity and quality of life.[95] The first clinical trial showing a benefit of treatment of PH in patients with HFpEF compared 1 year of sildenafil therapy with placebo and assessed for hemodynamic improvement in 44 patients with heart failure, diastolic dysfunction, EF > 50%, and pulmonary artery systolic pressure > 40 mm Hg.[97] Treatment with sildenafil led to an improvement in pulmonary hemodynamics and right ventricular performance as well as to LV relaxation.

Ongoing Clinical Trials

Two trials investigating drugs targeting the nitric oxide and cyclic guanine monophosphate pathway in the HFpEF population are currently under way. The

Table 5—*Randomized Placebo Controlled Trials on the Efficacy of Pulmonary Vasodilators in HF*

Medication	Disease	No. Patients	Primary End Point	Outcome
Epoprostenol[64]	HFrEF	471	Survival	Strong trend toward decreased survival
Bosentan[33]	HFrEF	1,600	Survival, HF hospitalizations	No improved survival
Bosentan[34]	HFrEF	94	Systolic PAP	No improved hemodynamics
Bosentan[32]	HFrEF	370	Change in clinical status	Terminated because of safety concerns
Sildenafil[95]	HFrEF	34	Peak $\dot{V}O_2$	Increased peak $\dot{V}O_2$ Reduced PVR Increased CO Reduced hospitalizations Improved 6MWD
Sildenafil[96]	HFrEF	46	Exercise capacity	Reduced systolic PAP Improved exercise ventilation
Sildenafil[97]	HFpEF	44	mPAP	Decreased mPAP

6MWD = 6-min walk distance; CO = cardiac output; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; $\dot{V}O_2$ = oxygen consumption (exercise capacity). See Table 3 and 4 legends for expansion of other abbreviations.

RELAX (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure) trial is evaluating the effect of 6 months of sildenafil vs placebo on exercise capacity, functional status, and ventricular function in patients with diastolic heart failure (EF > 50%). The DILATE (A Study to Test the Effects of Riociguat in Patients with Pulmonary Hypertension Associated With Left Ventricular Diastolic Dysfunction) trial is investigating the efficacy, safety, and pharmacokinetic profile of the novel agent riociguat, a stimulator of soluble guanylate cyclase, on mean PAP in patients with symptomatic PH due to LV diastolic dysfunction.

There are two other ongoing trials examining the utility of endothelin receptor antagonists in HFpEF-associated PH. The BADDHY (Safety and Efficacy of Bosentan in Patients with Diastolic Heart Failure and Secondary Pulmonary Hypertension) trial is investigating the effect of 12 weeks of bosentan on 6-min walk distance, hemodynamics, and quality of life in patients with PH and a PCWP > 15 mm Hg. The Safety and Efficacy Trial to Treat Diastolic Heart Failure Using Ambrisentan will investigate the safety of ambrisentan given for 16 weeks, with secondary outcomes being 6-min walk distance, WHO functional class, and 36-Item Short Form Health Survey scores.

Mechanical Support

Mechanical support in PH associated with HFrEF has been another area of study. Consistently, studies have shown that left ventricular assist device (LVAD) support reverses fixed or medically unresponsive PH and allows patients with HFrEF and PH to be eligible for orthotopic heart transplantation.[98-101] Post-transplant survival for patients with HFrEF and PH treated with LVAD does not differ from those patients without PH who receive LVAD.[102,103] Thus, in addition to other medical therapy, patients with HFrEF may benefit from further reduction of pulmonary pressures with mechanical support.

Summary

PH due to LHD is the most common type of PH encountered in western countries. 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. There is no consensus on what level, if any, of PAP or PVR should be considered disproportionate or out of proportion with the underlying cardiac conditions. At this time, the fundamentals of therapy for WHO group 2 PH are to optimize treatment of underlying conditions. Clinical studies on PAH-specific therapies have been disappointing, although small studies suggest that phosphodiesterase-5 inhibitors may be beneficial. More studies are required and some are currently under way 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 much-needed new therapeutic approaches can be developed.

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