ORIGINAL ARTICLE

The Failing Right Ventricle: An Internist's Guide to the Diagnosis and Management of Pulmonary Hypertension.

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Pulmonary hypertension represents a complex and multifactorial disease with significant implications on patients' morbidity, mortality, and quality of life. The number of patients hospitalized with pulmonary hypertension is increasing. Elevated pulmonary artery pressures as estimated by transthoracic echocardiogram are most commonly associated with left heart disease; however, careful attention and screening must be performed to promptly identify patients who may benefit from pulmonary vasodilator treatment. Early recognition and diagnosis of pulmonary hypertension is very important, but it can be challenging due to the nonspecific nature of patient symptoms and clinical findings. Furthermore, transthoracic echocardiogram does not always accurately estimate pulmonary artery pressures. Other clinical assessment tools such as computed tomography (CT) angiography of the chest and brain-type natriuretic peptide (BNP) levels can be helpful. Pulmonary hypertension is ultimately defined hemodynamically as a mean pulmonary artery pressure >20 mmHg, which is measured by right heart catherization. Following diagnostic evaluation, management of pulmonary hypertension and right ventricular failure focuses on optimizing right ventricular preload, afterload and contractility. A goal-directed approach to therapy helps guide treatment, and it helps identify patients who need escalation of therapy when goals are not being met. A goal-oriented approach to management improves outcomes and delays progression of pulmonary hypertension.

Keywords: pulmonary hypertension, dyspnea, right ventricular failure, angiography, riociguat

INTRODUCTION

Pulmonary hypertension represents a complex and challenging disease that significantly impacts patients from the perspective of morbidity, mortality, and quality of life. In recent years, hospital admissions in which primary or secondary pulmonary hypertension was the primary diagnosis has risen from 12,066 in 2000 to 13,605 in 2013. The average duration of hospital stay was 7 days with a total adjusted annual cost of approximately $900 million (1). Furthermore, pulmonary hypertension is frequently identified incidentally in patients undergoing echocardiogram for any reason. According to the Armadale study, approximately 1 in 9 patients who undergo transthoracic echocardiogram will have a diagnosis of primary or secondary pulmonary hypertension, which was defined in the study as an estimated pulmonary artery pressure (ePAP) >40 mmHg.

Interestingly, those who had an ePAP >40 mmHg also had a mean time to death of 4.1 years regardless of the cause of pulmonary hypertension (2). Hence, early recognition and management of pulmonary hypertension is critical, especially for the hospitalist, who is frequently caring for these patients in the hospital setting.

DIAGNOSIS

Right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension. The World Symposium on Pulmonary Hypertension recently convened and changed the diagnostic criteria for pulmonary hypertension to a mean pulmonary artery pressure (mPAP) >20 mmHg(3). Hemodynamically, pulmonary hypertension can be further categorized into pre-capillary and post-capillary groups. Patients with pre-capillary pulmonary hypertension have a mPAP>20 mmHg, a pulmonary vascular resistance (PVR)>3 woods units, and a pulmonary capillary wedge pressure (PCWP) <15mmHg. Post-capillary pulmonary hypertension is classically associated with left heart disease and is defined by mPAP>20mmHg, PVR<3 woods units, and a PCWP >15mmHg. The World Health Organization (WHO) further organizes pulmonary hypertension into 5 groups (Figure 1). The WHO groups of pulmonary hypertension can be characterized hemodynamically as shown in Figure 2. The WHO classification has attempted to organize the various causes of pulmonary hypertension into groupings with a similar pathophysiologic mechanism. WHO group 1, also known as pulmonary arterial hypertension (PAH) or primary pulmonary hypertension, is predominantly caused by vascular inflammation, remodeling, vasoconstriction and thrombosis in situ.(4) The pathophysiology of WHO groups 2, 3, 4, and 5 are much more heterogenous and complex, but many pathologic similarities exist between PAH and the other pulmonary hypertension groups.(5)

CHALLENGES IN DIAGNOSIS

The clinical presentation and symptoms associated with pulmonary hypertension are generally vague and nonspecific. The most common symptom amongst patients with pulmonary hypertension is dyspnea(6). Other common symptoms include fatigue and weakness. Clinical signs commonly associated with pulmonary hypertension and right ventricular failure such as leg edema, ascites and other typical heart failure findings occur in the advanced stages of pulmonary hypertension (6). Therefore, recognizing and diagnosing pulmonary hypertension early requires careful attention and vigilance on the part of the clinician.

The initial screening test recommended for evaluating patients with pulmonary hypertension is transthoracic echocardiography(TTE). The TTE is used to assess right ventricular structure, right ventricular systolic function and to estimate pulmonary artery pressures. Multiple echocardiographic parameters can be used to estimate pulmonary artery pressure as well as right ventricular pressure and function. These include tricuspid regurgitant velocity, right ventricular size, interventricular septal function, inferior vena cava diameter and fluctuations with respirations, right atrial area, pattern of systolic flow velocity and early diastolic pulmonary regurgitant velocity, and diameter of the pulmonary artery(7). While TTE is a very useful tool, the estimation of pulmonary artery pressure has been reported to be inaccurate in up to 48-50% of patients(8,9). Most common inaccuracies are from under-estimation (10). Therefore, the results of a TTE must be

interpreted in the context of a patient's clinical signs or symptoms.

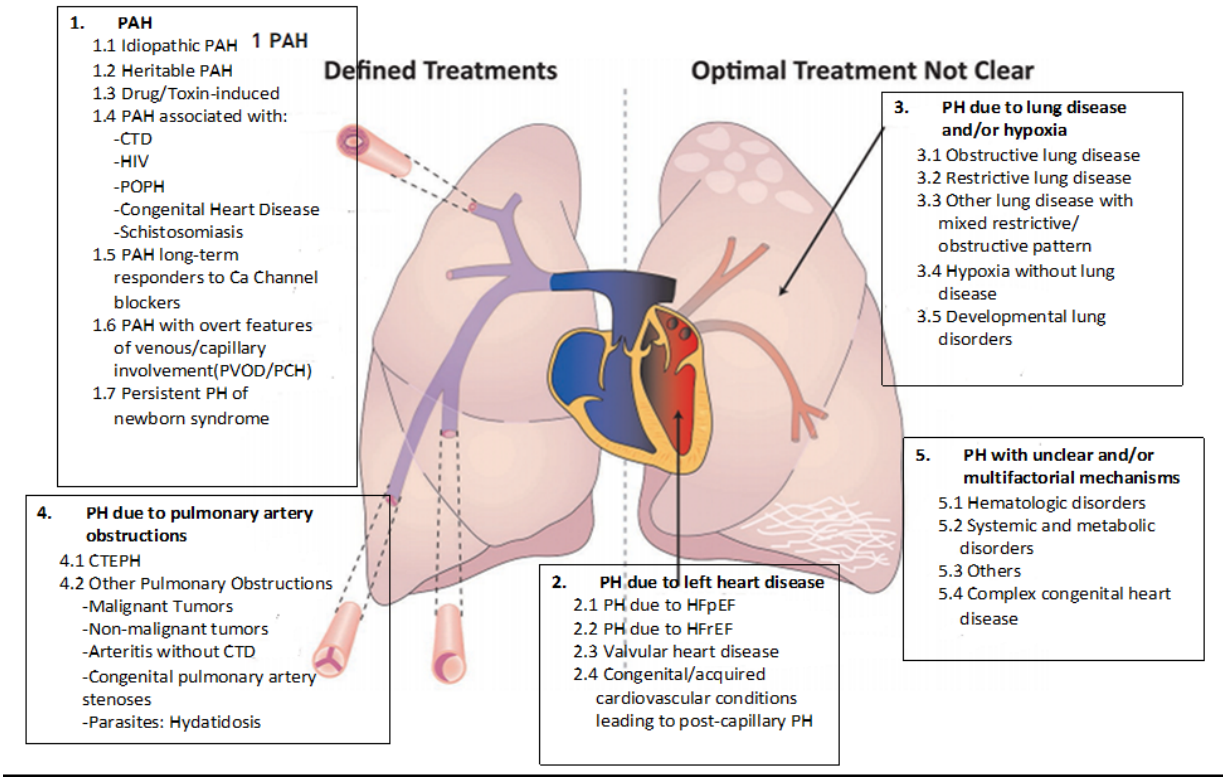

Figure 1. This chart summarizes the different types of pulmonary hypertension as defined by the World Health Organization. Figure was modified from the original published by Condliffe R, et al. (F1000Prime Rep. 2015 Jan 5;7:06.)

A normal ePAP on TTE does not necessarily exclude pulmonary hypertension in the appropriate clinical setting. Additional imaging may be necessary or should be considered to help confirm the presence of pulmonary hypertension.

Computed tomography (CT) angiography of the chest is often performed in many patients with pulmonary hypertension to assess for pulmonary embolism. When a CT angiography of the chest is available for review, the information from the images allows the clinician to assess changes in the pulmonary vasculature, the lung parenchyma as well as cardiac size and structure. This information can be used to identify clinical features consistent with a diagnosis of pulmonary hypertension. When evaluating the pulmonary vasculature, the CT chest can provide helpful measurements of the pulmonary artery-to-aorta ratio, the pulmonary artery diameter, and reflux of contrast into the hepatic veins and inferior vena cava.(11) An increased pulmonary artery diameter to ≥2.9cm is considered abnormal and suggestive of pulmonary hypertension(12). Furthermore, a pulmonary artery-to-aorta diameter ratio of ≥ 1.0 is abnormal and may be used to identify patients who may have pulmonary hypertension(13).

In addition to using CT angiography of the chest for evaluating the pulmonary vasculature, it can also be used to assess the right ventricle-to-left ventricle (RV-to-LV)

ratio and the right atrial (RA) size. An RV-to-LV ratio >.9 is considered abnormal and is suggestive of RV enlargement. On average, the RV-to-LV ratio in patients with pulmonary hypertension is 1.25(11). The RA size can be measured from the tricuspid annulus to the superior right atrial margin which is considered the long axis. A normal RA size in the long axis is estimated to be 3.4-5.3 cm.(14) In pulmonary hypertension patients, the RA size has been shown to average approximately 5.5 cm in the long axis(11). These measurements of RV and RA size can help identify patients who may have pulmonary hypertension.

Lastly, CT angiography of the chest can be used to assess for parenchymal changes. Ground glass opacities have been shown to be present in approximately 40% of patients with a diagnosis of primary pulmonary hypertension. The most predominant pattern of the ground glass opacities is centrilobular, but any pattern of ground glass can be suggestive of primary pulmonary hypertension in the appropriate clinical setting(11). Ground glass opacities can also be seen in patients with secondary pulmonary hypertension, but the exact frequency and incidence is not well established.

In addition to TTE and CT chest, BNP is another noninvasive marker with multiple benefits in the setting of pulmonary hypertension. This lab marker has been shown to correlate with right ventricular structure and function in patients with pulmonary hypertension. BNP showed a sensitivity of 100% and specificity of 94% in detecting right ventricular systolic dysfunction when the pro-BNP was >1685 pg ml-1(15). The BNP is also predictive of mortality and poor outcomes in patients with pulmonary hypertension. Hence, BNP can be a useful tool when combined with clinical suspicion and cardiac imaging for identifying patients with a high likelihood of having a diagnosis of pulmonary hypertension.

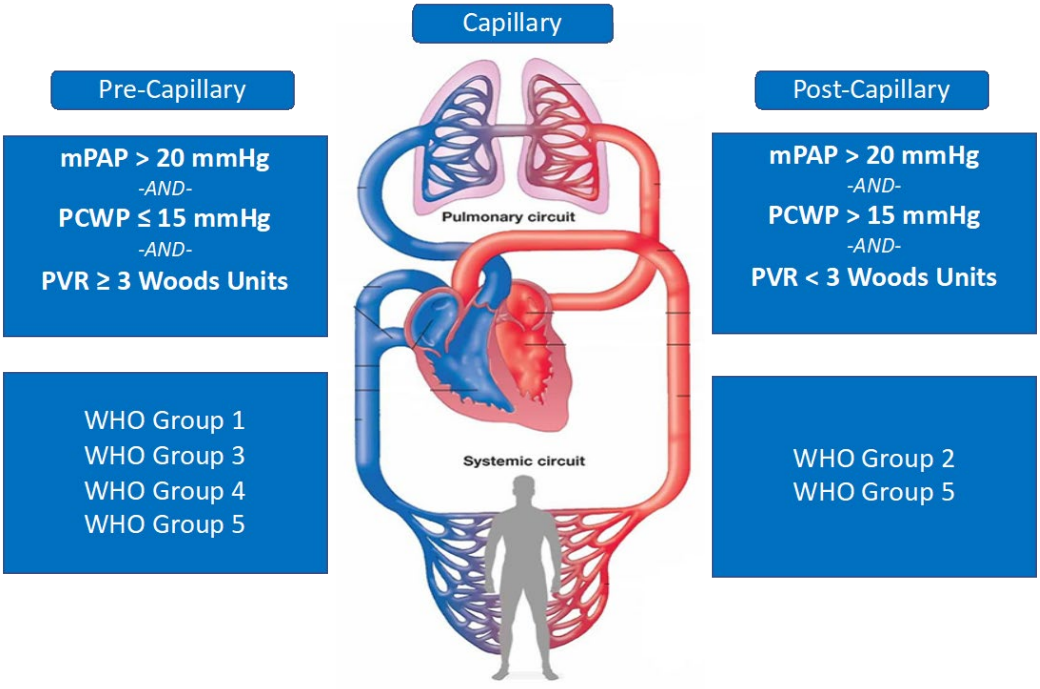

Figure 2. Summarizes the most updated definition of pulmonary hypertension. Also, includes the pulmonary hypertension groups and how they can be organized from the perspective of hemodynamics.

RISK ASSESSMENT

Making the decision to pursue right heart catheterization requires a thorough clinical evaluation including a detailed history, physical exam and risk assessment. Since multiple WHO groups of pulmonary hypertension have a similar hemodynamic definition as shown in figure 2, differentiating the types relies heavily on risk assessment and screening. Careful attention must be made to identify patient groups who are high risk for having pulmonary arterial hypertension (WHO group I) or chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) since these two groups benefit most from vasodilator therapy. Right heart catheterization is generally reserved for patients with high risk of having a pulmonary hypertension type that would benefit from vasodilator therapy. The most recent guidelines recommend routine screening in all patients with a diagnosis of pre-capillary pulmonary hypertension for connective tissue disease, hepatitis and human immunodeficiency virus (HIV) (16). History of past medication use including weight loss supplements and illicit drug use is also extremely important. Detailed family history should be obtained to identify patients who may have hereditary pulmonary hypertension.

Right heart catheterization should be aggressively pursued in patients with significant risk factors for WHO group 1 pulmonary hypertension since these patients are likely to benefit from early vasodilator therapy. In other words, patients with a known history of HIV, connective tissue disease, liver cirrhosis, high risk drug exposures, family history of pulmonary hypertension, and congenital heart disease should undergo regular screening and right heart catheterization to detect pulmonary hypertension early. The same principle of early detection and invasive diagnostic assessment applies for patients with a ventilation-perfusion (VQ) scan that is high probability for pulmonary embolism when chronic thromboembolic disease is being considered. These two groups of pulmonary hypertension benefit most from early and aggressive vasodilator therapy. In the case of CTEPH, vasodilator therapy functions as a bridge to more definitive surgical intervention depending on the anatomic location of the pulmonary emboli. For patients with pulmonary hypertension due to left heart disease or chronic lung disease, risk assessment algorithms should be used to determine if early right heart catheterization is necessary.

The most recent pulmonary hypertension guidelines suggest evaluating patients for risk factors that increase the pre-test probability for left heart disease as the cause of pulmonary hypertension (Table 1) before pursuing right heart catheterization (16). If the patient has high probability risk factors including >70 years old, previous cardiac intervention, atrial fibrillation, structural left heart disease, electrocardiogram (EKG) evidence of left bundle branch block or left ventricular hypertrophy (LVH), left atrial dilation, obesity, hypertension, dyslipidemia, and diabetes; then, the patient has a high likelihood of having an underlying WHO group 2 pulmonary hypertension due to left heart disease. These patients with left heart disease have not been shown in clinical trials to consistently derive a significant benefit from vasodilator therapy. Therefore, treatment for pulmonary hypertension due to left heart disease is targeted toward optimizing the underlying left heart problem with traditional heart failure medications or interventions where appropriate. Patients who are intermediate or low probability of having left heart disease based on the

aforementioned risk factors should undergo right heart catheterization.

Table 1. Recommended pre-test probability assessment in patients with pulmonary hypertension. Patients with high probability of left heart disease do not necessarily need to undergo right heart catheterization. High probability patients should undergo aggressive optimization of left heart disease. Patients who are intermediate or low probability for left heart disease should be strongly considered for right heart catheterization in the appropriate clinical setting.[16]

Table 1 Pre-test probability assessment of left heart disease phenotype			
Feature	High Probability	Intermediate probability	Low probability
Age	>70 year	60-70 years	<60 years
Obesity, systemic hypertension, dyslipidemia, glucose intolerance/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
EKG	left bundle branch block or left ventricular hypertrophy	mild left ventricular hypertrophy	normal or signs of right ventricular strain
Echocardiography	left atrial dilation; grade >2 mitral flow	no left atrial dilation; grade <2 mitral flow	no left atrial dilation; E/e' <13
Cardiac MRI	left atrial strain or LA/RA >1		No left heart abnormalities

A similar approach has been recommended when evaluating patients with underlying chronic lung disease who have evidence of pulmonary hypertension (Table 2) (15). Pulmonary vasodilators have not been shown to provide a significant clinical benefit in patients with pulmonary hypertension secondary to underlying chronic lung disease. Fortunately, the majority of patients with WHO group 3 pulmonary hypertension have mild to moderate severity pulmonary hypertension (17). WHO group 3 pulmonary hypertension rarely causes severely elevated pulmonary artery pressures. Patients with obstructive lung disease who have a forced expiratory volume (FEV1) <60% of predicted or patients with a restrictive lung disease with a forced vital capacity (FVC) <70% of predicted are likely to have pulmonary hypertension secondary to the underlying chronic lung disease. In addition to lung function testing, these patients should also undergo CT chest evaluation to determine the extent of underlying lung parenchymal changes. The lung function must be considered in the context of the underlying parenchymal changes to determine whether the chronic lung disease is severe enough to explain a patient's pulmonary hypertension.

APPROACH TO THE FAILING RIGHT VENTRICLE

The approach to optimizing right ventricular function focuses on optimizing preload, afterload and contractility, which is not much different than the approach to optimizing left ventricular function in the setting of left heart failure. Right ventricular preload is largely determined by right atrial pressure. A severely elevated right atrial pressure, especially relative to the pulmonary capillary wedge pressure, indicates a significantly congested right ventricle. Patients with an elevated right

ventricular preload and clinical signs of heart failure can benefit from diuresis to avoid further complications such as cardiorenal syndrome, cardiohepatic syndrome, and myocardial ischemia from poor coronary perfusion. The goal of diuresis in pulmonary hypertension and RV failure is to maintain a careful balance between sufficient preload for cardiac filling and also
provide relief from RV overload. Renal function should be monitored closely while patients are undergoing diuresis in the setting of acute or chronic renal dysfunction.

Right atrial pressures can be estimated using many noninvasive tools including TTE, bedside ultrasound of the inferior vena cava, and bedside assessment for jugular venous distention or lower extremity edema. As previously discussed, BNP levels correlate well with RV dysfunction in the appropriate clinical setting and can be useful when managing RV failure. Invasive tools to assess right atrial pressure include central venous pressure (CVP) measurement by means of a central venous catheter or by placing a Swan-Ganz Catheter and measuring the right atrial pressure directly. Of note, patients with acute right ventricular failure and an elevated right atrial pressure do not always benefit from a fluid bolus as is commonly assumed. In fact, the notion that RV failure is invariably preload dependent is an oversimplification (18). Depending on the clinical context, aggressive intravenous fluid administration in RV failure can actually worsen RV congestion, which would result in decreased RV function and ultimately compromise LV function. Fluid bolus administration should be used with caution in patients suspected of having pulmonary hypertension and RV failure.

RV afterload can be estimated by the mean pulmonary artery pressure and the pulmonary vascular resistance. Optimizing RV afterload largely depends on the underlying cause of the pulmonary hypertension. In the case of WHO group 1 pulmonary hypertension, the pulmonary selective vasodilators can be used in combination with diuresis if appropriate (9). There are currently a variety of approved pulmonary vasodilators that fall within one of three main pharmacologic pathways which include phosphodiesterase inhibitors, endothelial receptor antagonists, and prostacyclin analogues. Patients with idiopathic pulmonary arterial hypertension, hereditary pulmonary arterial hypertension, or drug-induced pulmonary arterial hypertension may benefit from calcium channel blockers if the vasoreactive testing is positive during right heart catheterization(9). Unfortunately, pulmonary vasodilators do not have a clearly established role or benefit in patients with WHO group 2 and 3 pulmonary hypertension. Hence, decreasing RV afterload in patients with WHO group 2 or 3 pulmonary hypertension focuses on optimizing the underlying disease process contributing to the pulmonary hypertension. In the setting of cardiogenic shock from severe RV failure, inotropic medications such as dobutamine and milrinone can also be used to decrease RV afterload. Inotropic support directly lowers PVR by increasing cardiac output. Diuretics can also be used in these patients when there are clinical signs of heart failure based on imaging results, laboratory data and physical exam findings.

Patients with acute or chronic pulmonary embolism need to have the clot burden removed with anticoagulation or procedural intervention if indicated. Riociguat is a soluble guanylate cyclase agonist and is the only vasodilator approved for the medical management of CTEPH. Patients with pulmonary hypertension from WHO group 5 should be evaluated by a pulmonary hypertension specialist to

determine the role of pulmonary vasodilators on a case-by-case basis.

Careful attention should also be placed on avoiding hypoxia and acidemia when the RV is decompensated because these abnormalities can cause an increase in pulmonary vascular resistance and a decrease in RV contractility. If needed, positive pressure ventilation can be used to optimize a patients acid-base balance; however, the benefit of positive pressure ventilation must be weighed with the risk of increasing the pulmonary vascular resistance from the effect of positive pressure on the mediastinal structures (19).

Table 2. Outlines the risk factors that suggest the pulmonary hypertension is likely due to underlying chronic lung disease.[15]

Table 2 Pre-test probability assessment of chronic lung disease		
Features	Severe Chronic Lung Disease(high probability)	Limited Chronic Lung Disease(low probability)
Obstructive lung disease	FEV1<60% predicted	FEV1>60% predicted
Restrictive lung disease	FVC<70% predicted	FVC>70% predicted
CT chest findings	extensive parenchymal changes	minimal parenchymal changes

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Figure 3. Demonstrates many of the goals that pulmonary hypertension treatment should be working toward achieving. (Reproduced with permission of the © 2020 European Society of Cardiology & European Respiratory Society. *European Respiratory Journal 46 (4) 903-975; 30 September 2015*

GOAL-DIRECTED TREATMENT

With the use of risk stratification tools, goals of therapy for pulmonary hypertension patients can be monitored closely, and treatment can be escalated promptly when management goals are not being met. Commonly monitored clinical parameters in pulmonary hypertension patients include WHO functional class, 6-minute walk distance, peak oxygen consumption (VO2) from cardiopulmonary exercise testing, BNP levels, and TTE parameters including right atrial area and presence of pericardial effusion (Figure 3). Ideally, goal-directed treatment should be used to target a WHO

functional class of 1-2, a 6-minute walk distance >440m, pro-BNP<300, a peak VO2>15 mL/min/kg, a right atrial area <18cm^2(9). When these parameters are not able to be met, treatment intensity may need to be escalated.

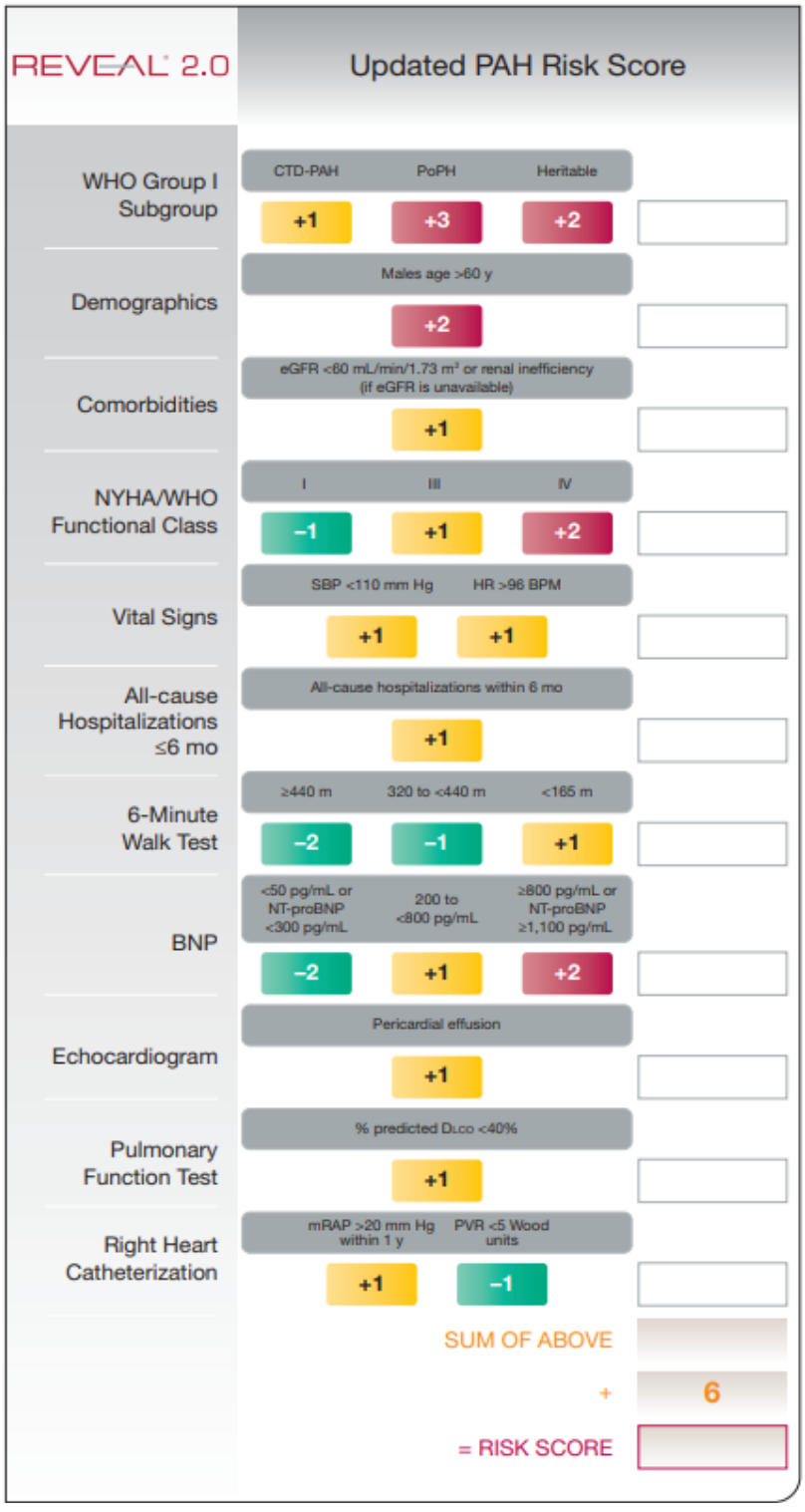

Figure 4. Risk calculator developed by the REVEAL registry to risk stratify patients with PAH and help guide therapy.

Another important risk assessment tool for PAH was developed from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL)(20)(Figure 4). From this registry, the REVEAL score was developed and has recently undergone an update. This risk assessment tool can be used to target a low risk score ≤ 6. When goal-oriented therapy is used to guide management, mortality in patients with pulmonary hypertension has been shown to improve when followed over 3 years. Furthermore, early treatment initiation and titration in patients with PAH has been shown to delay progression of the disease (21).

CONCLUSION

Pulmonary hypertension represents a complex and multifactorial disease process with significant morbidity and mortality implications for patients. Pulmonary hypertension is frequently identified on TTE and is most commonly due to left heart disease. Patients with significant risk factors for PAH and CTEPH should be screened with TTE and undergo early right heart catheterization to ensure timely treatment initiation. The management of right ventricular failure from pulmonary hypertension focuses on optimizing RV preload, afterload and contractility. Once pulmonary hypertension is identified and treatment is initiated, a goal-oriented approach using established risk calculators can improve mortality outcomes and delay clinical worsening.

Notes

Potential conflicts of interest: Author declares no conflicts of interest.

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