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# Pulmonary arterial hypertension and associated conditions



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## Part 1: The classification and diagnosis of PAH

### *Definition and epidemiology*

Pulmonary hypertension (PH) refers to an increase in pulmonary arterial pressure, defined as mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg at rest, that if left untreated may progress to right ventricle dysfunction and failure.<sup>1</sup> Worldwide, pulmonary hypertension associated with schistosomiasis is considered the most common form of the disease.<sup>2</sup> In the United States, post-capillary pulmonary hypertension due to left heart disease is the most prevalent form of PH.

Pulmonary arterial hypertension (PAH) is a form of pre-capillary pulmonary hypertension that is defined based on cardiopulmonary hemodynamics as a mPAP  $\geq 25$  mmHg, pulmonary artery occlusion pressure (PAOP)  $\leq 15$  mmHg, and pulmonary vascular resistance (PVR)  $\geq 3$  Wood units (WU) at rest.<sup>1</sup> According to the latest classification by the World Symposium in Pulmonary Hypertension (WSPH), this group of pre-capillary pulmonary hypertension, termed Group 1 PAH, consists of idiopathic pulmonary arterial hypertension (IPAH) and heritable PAH (HPAH) that occur in the absence of any identifiable cause, and PAH associated with other conditions such as the use of anorexigens and other drugs, schistosomiasis infection, connective tissue diseases, congenital heart disease, HIV, or chronic liver disease.<sup>3</sup> IPAH and HPAH are rare, with an estimated incidence of 1–2 cases per million in the general population according to the REVEAL registry.<sup>4</sup>

Historically, the first report of PAH dates back to 1891 by Ernst von Romberg who described findings of “pulmonary vascular stenosis” on autopsy. However, it was not until the 1970s with the recognition of fenfluramine/phentermine (also known as fen-phen)-associated PAH,<sup>5</sup> that prompted the first WSPH meeting to address, describe, and classify PH. Since then, great strides have been made in the advancement of research and management of this disease.

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**Table 1**

The 2013 fifth world symposium on pulmonary hypertension classification of pulmonary hypertension.

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Pulmonary arterial hypertension
Idiopathic PAH
Heritable PAH
BMPR2
ALK-1, ENG, SMAD9, CAV1, KCNK3
Unknown
Drug and toxin induced
Associated with
Connective tissue disease
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
<i>Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</i>
<i>Persistent pulmonary hypertension of the newborn (PPHN)</i>
Pulmonary hypertension due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Pulmonary hypertension due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Chronic thromboembolic pulmonary hypertension (CTEPH)
Pulmonary hypertension with unclear multifactorial mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

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BMPR2, bone morphogenic protein receptor type 2; ALK-1 activin-like receptor kinase 1, SMAD9, mothers against decapentaplegic 9; CAV1, caveolin-1, ENG, endoglin; KCNK3, potassium channel super family K member-3; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

### Classification

The most recent Fifth WSPH held in Nice, France, in 2013 revised the classification of pulmonary hypertension disorders according to the etiologies clinical, hemodynamic, and pathological findings.<sup>3</sup> Pulmonary hypertension is divided into five broad categories (Table 1): Group 1 PAH, Group 2 pulmonary hypertension secondary to left sided heart disease, Group 3 pulmonary hypertension secondary to chronic lung disease or hypoxia, Group 4 chronic thromboembolic pulmonary hypertension, and Group 5 pulmonary hypertension secondary to miscellaneous and multifactorial causes. The most notable updates include the addition of pediatric conditions such as persistent pulmonary hypertension of the newborn (PPHN) within Group 1 and moving chronic hemolytic anemia-related pulmonary hypertension to Group 5.

### Physiology

The pulmonary vasculature bed is a low-pressure, low-resistance, high-capacitance system that can easily accommodate increases in cardiac output, for example during stress and exercise,

with minimal elevation in the pulmonary artery pressures. A normal mPAP is approximately  $14 \pm 3$  mmHg, with an upper limit of normal around 20 mmHg.<sup>6</sup>

An elevated mPAP can develop as a result of a hyperkinetic state due to a rise in cardiac output (CO), changes within the pulmonary arterial vasculature resulting in increased PVR (pre-capillary PH), a passive process due to elevated left heart chamber pressures resulting in elevated PAOP (post-capillary PH), or a combination of these changes. This is better understood by applying Ohm's electric law (flow = change in pressure/resistance) to the pulmonary vasculature system.<sup>7</sup>

$$CO = (mPAP - PAOP) / PVR$$

This equation can be rearranged to display how the mPAP is influenced by these other cardiopulmonary variables

$$mPAP = (CO \times PVR) + PAOP$$

### *Pathogenesis of PAH*

The pathogenesis of Group 1 PAH is complex, multifactorial, and remains unclear. Vasoconstriction, vascular remodeling, and thrombosis characterize the vasculopathy that contributes to the elevated PVR observed in PAH. Excessive vasoconstriction occurs as a result of abnormal function and expression of potassium channels and endothelial dysfunction. Abnormal proliferation of endothelial cells (plexiform lesions), smooth muscle cells, and fibroblasts occur as a result of an imbalance in various vasoactive mediators. These mediators include nitric oxide (NO), prostacyclin-I (prostacyclin), endothelin-1 (ET-1), serotonin, thromboxane, and other chemokines produced by the dysfunctional endothelium.<sup>8</sup> The dysfunctional pathways observed in PAH result in intimal and medial hypertrophy, intimal fibrosis, and in situ thrombosis of the small-to-medium-sized pulmonary arteries and arterioles.<sup>9</sup> Targeted-PAH pharmacotherapy, including medications that augment the nitric oxide, prostacyclin pathways, and inhibit endothelin-1 pathway, has been the crux for managing this disease state.

### *Genetics*

Various genetic mutations and variants have been recognized in the last decade to play a role in the pathogenesis of HPAH. Of these, heterozygous mutations in bone morphogenic protein receptor type 2 (BMPR2), a member of the transforming growth factor- $\beta$  (TGF- $\beta$ ) family, has been identified in approximately 75% of all familial PAH, as well as in 25% of sporadic PAH cases.<sup>10</sup> Mutations in other genes in the TGF- $\beta$  family, activin-like receptor kinase 1 (ALK-1), and endoglin (ENG) have also been described in patients with hereditary hemorrhagic telangiectasia with PAH.<sup>11</sup> More recently, genetic mutations in mothers against decapentaplegic homolog-9 (SMAD9), caveolin-1 (CAV1), T-box transcription factor-4 (TBX4), and potassium channel super family K member-3 (KCNK3) have been recognized in families with multiple affected members, providing more insight into the pathogenesis of PAH.<sup>12</sup>

HPAH accounts for 3% of all cases of PAH.<sup>4</sup> The existence of two affected family members with PAH, or the identification of PAH genetic mutations in a patient with the disease (regardless of family history), is needed to make a diagnosis of heritable PAH. The usual age of diagnosis in adults is in the mid-30s. Counseling family members with heritable PAH is challenging. All PAH genes are transmitted in an autosomal dominant fashion with variable penetrance, with female predominance in those where the BMPR2 mutation is identified.<sup>12</sup> That being said, 20% of PAH-associated genetic mutation carriers develop clinical disease.<sup>13</sup>

Heritable forms of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), a subtype of Group 1 PAH, have been recognized in consanguineous families suggesting an autosomal recessive inheritance. Bi-allelic mutations in eukaryotic translation initiation factor-2 alpha kinas-4 (EIF2AK4) have been identified on whole-exome sequencing in all familial cases and in 25% of sporadic cases.<sup>14</sup>

## Part 2: Evaluation of the patient with pulmonary hypertension

### *Clinical manifestations*

Patients with PH commonly present with nonspecific symptoms and may be initially evaluated for other causes of shortness of breath before a diagnosis of pulmonary hypertension is even considered. As such, delays in the correct diagnosis can occur resulting in manifestations of right ventricle dysfunction prior to referral to a pulmonologist or cardiologist. It is important to appreciate that the signs and symptoms of PH correlate to the progression of underlying right ventricle impairment.

The most common presenting symptoms in PH are fatigue, weakness, dizziness, and progressive shortness of breath with exertion. Patients may initially notice that they cannot keep up at the same pace as their peers, before progressing to shortness of breath while walking up inclines, bending over, climbing stairs, and in severe cases experiencing breathlessness while walking on a flat surface and while performing activities of daily living. With progressive disease, individuals may complain of lightheadedness, syncope, angina, and symptoms of right-sided heart failure that manifest as lower extremity and abdominal swelling. The World Health Organization (WHO) created a functional class scoring system to describe the symptomatic limitation in patients with pulmonary hypertension (Table 2), which serves to guide individualized treatment.<sup>15</sup>

In certain cases, symptoms secondary to pulmonary artery enlargement and extrinsic compression of different structures may occur. Chest pain as a result of left main coronary artery compression by an enlarged pulmonary artery may be mistaken for a symptom of coronary artery disease. Rarely, patients may also complain of hoarseness as a result of compression of the left recurrent laryngeal nerve by the pulmonary arteries, known as cardiovocal or Ortner's syndrome.

If the PH is secondary to an underlying condition (scleroderma, chronic lung disease, sarcoidosis, etc.) symptoms associated the condition will likely be present. As such, it is important to inquire about symptoms that may be associated with a systemic or connective tissue disease (sarcoidosis or scleroderma), symptoms of left-sided heart failure, liver dysfunction, or renal disease. Smoking exposure, travel history, and family history for potentially inherited disorders should be obtained. Various medications have been reported to cause or be associated with the development PAH (Table 3), therefore, a thorough history of exposure to prescribed medications, recreational drugs, chemotherapeutic agents, anorexigens, and toxins should be discussed in detail with the patient.

### *Physical examination*

As with every disease process, physical examination can reveal important clues in the work-up of patients with suspected PH. Select exam findings can contribute to the identification of PH etiology, determine disease severity, and guide overall management. The physical examination findings observed in PH are a reflection of elevated right ventricle volume and pressure. This section will focus on the physical examination findings characteristic of PAH.

Depending on disease severity, several clinical signs may be appreciated upon examination and auscultation of the heart. Right parasternal lift or heave may be palpated by resting the heel of the hand to the left of the sternum. If present this finding indicates right ventricular

**Table 2**

WHO Functional class assessment.

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WHO Class 1: no limitation of activity

WHO Class 2: shortness of breath with normal activities such as climbing stairs, or performing groceries

WHO Class 3: no shortness of breath at rest but occurs on performing basic activities of daily living

WHO Class 4: shortness of breath at rest

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**Table 3**  
Drug and toxin induced PAH.

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Interferon $\alpha$ and $\beta$
Dasatinib	Amphetamine-like drugs
	Selective serotonin reuptake inhibitors <sup>a</sup>
Likely	Unlikely
Amphetamines	Oral contraceptives
l-Tryptophan	Estrogen
Methamphetamines	Cigarette smoking

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<sup>a</sup> Selective serotonin reuptake inhibitor have been demonstrated as a risk factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in pregnant women exposed to SSRIs (especially after 20 weeks of gestation).

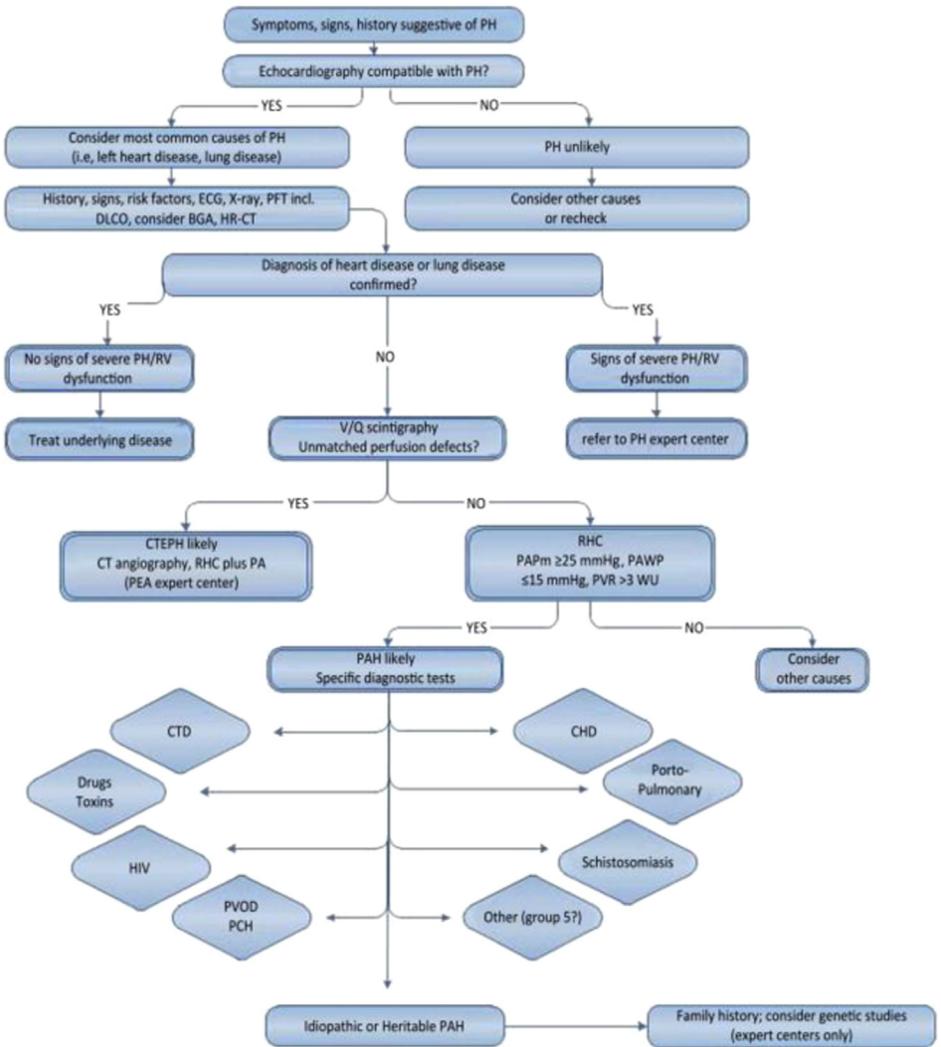
enlargement. A palpable tap (palpable pulmonary valve closure) can occasionally be felt by placing the fingers over the left second intercostal space (pulmonic area) in the setting of PH. Splitting of the second heart sound with a loud pulmonic valve component (P2) can be detected as a result of the forced closure of the pulmonic valve secondary to elevated pulmonary pressures. The murmur of tricuspid regurgitation is appreciated over the left fourth intercostal space, it is pansystolic, and augmented by inspiration. The presence of a third heart sound (S3) indicates increased right ventricle diastolic filling pressure, while a right fourth heart sound (S4) signifies decreased ventricular compliance.<sup>16,17</sup> Patients with right heart dysfunction may have elevated jugular venous pressure (JVP), lower extremity pitting edema, and in severe cases develop hepatomegaly and abdominal ascites. The presence of ascites may also be a finding of underlying liver disease. Auscultation of the lungs is usually unremarkable in PAH. The presence of bilateral crackles may indicate pulmonary edema that can occur in the setting of left heart dysfunction.

JVP distention is an indirect measure of central venous pressure that can give important clues during the physical examination. During examination, the patient should be at 45° angle and asked to turn their head to the left. A double waveform pulsation can be observed with JVP and vertical distance from the sternal angle is usually below 3 cm. A distended JVP indicates elevated central venous pressure that can occur in the setting of elevated right sided cardiac pressures and right ventricle dysfunction.<sup>18</sup> A discernable JVP can be further appreciated by applying pressure to the right upper quadrant to illicit the hepatojugular reflux sign.<sup>19</sup> Abnormalities in the JVP waveform may appear in certain conditions. A large a-wave can arise in the setting of pulmonary hypertension, while prominent v-waves with steep y-descent may be present in the setting of tricuspid regurgitation (TR). The rapid rise and fall of the JVP can sometimes be seen in TR, and is termed the Friedreich's sign; this is more commonly seen in the setting of constrictive pericarditis. In cases of severe TR, the c- and v-waves may merge to form a cv-wave, which occurs simultaneously along with the carotid pulse. A paradoxical increase in JVP during inspiration, also known as the Kussmaul's sign, indicates right ventricle filling impairment that can occur in the setting of severe right ventricular failure, a significant pericardial effusion, right ventricular infarction, constrictive pericarditis, or tricuspid stenosis.

The presence of clubbing can be observed in the setting of PVOD, congenital heart disease, or interstitial lung disease-associated PH, but is usually absent in other forms of PAH. Digital ulcers, Raynaud's phenomena, and tight skin over the knuckles exist in the setting of scleroderma; while telangiectasia and icteric sclera may be present in cirrhosis. Evaluation for systemic features of other diseases associated with PAH is essential in determining the underlying cause.

Work-up

In the evaluation and work-up of the patient with suspected PH, several tools can help guide diagnosis and decision-making. Right heart catheterization (RHC) remains the gold standard test in confirming the diagnosis of PH and differentiating between pre-capillary PH, post-capillary PH, and mixed PH with both pre-capillary and post-capillary disease. A stepwise diagnostic approach to PH evaluation has been proposed in the most recent Nice guidelines (Fig.).<sup>1</sup>



**Fig.** Diagnostic algorithm for pulmonary hypertension. Reproduced from Hoeper et al.<sup>1</sup> with permission from Elsevier. BGA, blood gas analysis; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity of the lung for carbon monoxide; ECG, electrocardiogram; HR-CT, high-resolution computed tomography; PA, pulmonary angiography; PAH, pulmonary arterial hypertension; PAPm, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary hemangiomas; PEA, pulmonary endarterectomy; PFT, pulmonary function testing; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheter; RV, right ventricle; V/Q, ventilation/perfusion; X-ray, chest radiograph.



**Image 1.** CXR showing enlarged pulmonary arteries in a patient with IPAH.

### *Chest radiography*

The chest radiograph (CXR) may provide clues suggestive of PH and other associated conditions. At the time of presentation, 90% of PH patients will have an abnormal CXR finding. Enlarged pulmonary arteries, dilated right atrium, and attenuation of peripheral pulmonary vasculature markings (also known as pruning) are often present in the setting of PH.<sup>20</sup> The finding of asymmetrical oligemia on CXR may suggest chronic thromboembolic pulmonary hypertension (CTEPH). On lateral views, the retrosternal space may be absent due to an enlarged right ventricle (Images 1 and 2).

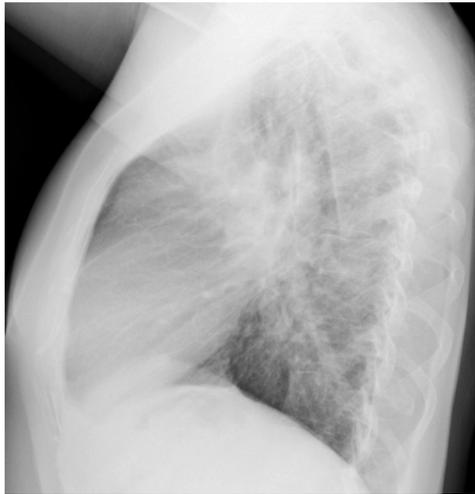
The findings of distended lungs and flattened diaphragm may indicate underlying chronic obstructive pulmonary disease (COPD), while prominent reticular thickening may suggest an interstitial lung disease (ILD) process. In patients with congestive heart failure, congenital heart disease, and PVOD/PCH signs of venous congestion may be present: an enlarged cardiac silhouette, pulmonary edema, Kerley-B lines, and pleural effusions.

### *Electrocardiogram*

The electrocardiogram (ECG) manifestations of PH correspond to increased right-sided heart strain and overload (Image 3). Findings of right axis deviation, tall right pericardial R-waves, and right bundle branch block may indicate right ventricle hypertrophy or dilation, while an enlarged P-waves in lead II signifies right atrial enlargement.<sup>21</sup> Physicians should be aware that while these findings may have a good positive predictive value for right heart strain, their absence does not exclude the presence of PH.<sup>22</sup>

### *Pulmonary function tests*

Pulmonary function tests (PFTs) are an important component in the evaluation of shortness of breath in PH. Significant findings of obstructive or restrictive ventilator defects suggest an underlying pulmonary process as the etiology of PH (Group 3 PH), such as COPD or ILD respectively. Mild reductions in spirometry and lung volume values are often present in PAH but these findings do not correlate to the severity of symptoms. Most commonly, an isolated reduction in diffusion capacity of the lung for carbon monoxide (DLCO) is present suggesting the



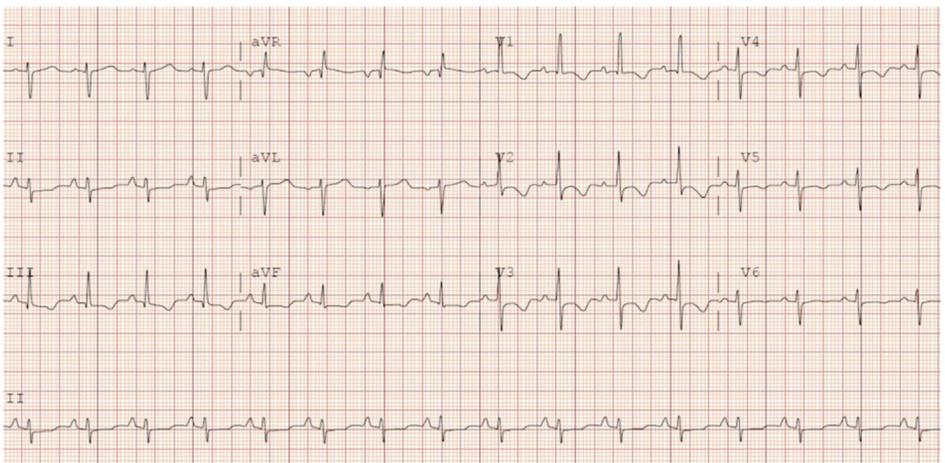
**Image 2.** Lateral CXR showing an absent retrosternal space in a patient with IPAH.

presence of PAH.<sup>23</sup> A significant reduction in DLCO may sometimes occur in the setting of PVOD/PCH. In patients with CTD-PAH and underlying ILD, the ratio of the forced vital capacity (FVC%) to DLCO% > 1.8 has been shown to help distinguish CTD-PAH from Group 3 PH secondary to ILD, where the FVC%/DLCO% is expected to be around 1.0.<sup>24</sup>

### Computed tomography imaging

A contrasted computed tomography (CT) angiography chest scan can provide important clues that may suggest the presence of PAH, Group 2 PH by the finding of enlarged left cardiac chambers, or identify parenchymal disease such as emphysema and interstitial lung disease.

An enlarged main pulmonary artery (PA) is often present in the setting of PAH (*Image 4*); the normal size is on average 29 mm in men and 27 mm in women based on the Framingham Heart Study.<sup>25</sup> The absence of an enlarged PA however does not exclude PH. Physicians should be



**Image 3.** ECG of a patient with pulmonary arterial hypertension showing signs of right atrial enlargement and right heart strain.

aware that PA dilation could also occur in the absence of PAH, as a normal variant in young females or in association with other conditions that may include connective tissue diseases, left-to-right shunting, pulmonary artery aneurysm, or idiopathic dilatation.<sup>26</sup> To correctly measure the diameter of the main PA, the measurement should be taken lateral to the ascending aorta, at the level of PA bifurcation, as a right angle to the long axis of the pulmonary vessel.<sup>27</sup> The intraluminal diameter is measured in contrasted studies while in non-contrasted studies the PA vessel wall is included during measurement. If the ratio of the main PA diameter to the ascending aorta diameter is greater than 0.9, this has been suggested to be a more specific finding for PAH.<sup>25,27</sup>

The CT scans may also identify the presence of a pulmonary artery filling process in thromboembolic disease, pulmonary arteriovenous malformations, pulmonary aneurysms, bronchial collateral, pulmonary vessel stenosis to extrinsic compression, or pulmonary vein stenosis.<sup>28</sup>

Cardiac signs of PH include enlarged or dilated right heart chambers, a right ventricle to left ventricle ratio  $> 0.9$ , right ventricular hypertrophy (free wall right ventricle thickness  $> 4$  mm), flattening or bowing of the interventricular septum toward the left ventricle, dilated inferior vena cava and reflux of contrast material into the hepatic veins.<sup>29,30</sup> The presence of pericardial effusion indicates severe PH and implies a worse prognosis.

Mosaic attenuation may be observed in PAH and is visualized as patchy areas of different attenuation indicating decreased perfusion in the setting of PH.<sup>31</sup> This finding is more common in CTEPH but can be found in approximately 12% of patients with PAH.<sup>32</sup> Poorly defined centrilobular ground glass nodules can be seen in the setting of IPAH, PVOD, and PCH. Histological analysis has revealed that centrilobular ground glass nodules reflect the presence of cholesterol granulomas.<sup>33</sup>

### Echocardiography

Transthoracic echocardiography (ECHO) is the recommended noninvasive tool for screening and early detection of PH.<sup>20</sup> It can estimate right ventricle systolic pressures (RVSP); provide an anatomical and functional assessment of the heart chambers and cardiac valves; and screen for the presence of intracardiac or intrapulmonary shunting.<sup>34</sup>

Doppler ECHO is used to determine the presence of underlying valvular heart disease, measure the peak jet velocity across the TR,<sup>35</sup> and estimate left ventricle ejection fraction (EF). A normal EF ( $\geq 45\%$ ) can be used to rule out systolic heart failure as an etiology of PH. In the setting of normal mitral valve function and normal EF, an enlarged left atrium ( $> 3.8$  cm) may indicate the presence of underlying heart failure with preserved ejection fraction (HFpEF).<sup>36</sup>

The right atrial pressure (RAP) can be estimated by measuring the inferior vena cava (IVC) diameter and collapsibility.<sup>37</sup> Along with the TR peak jet velocity ( $v$ ), the RVSP can be estimated



**Image 4.** Contrasted CT chest scan showing an enlarged pulmonary artery in a patient with connective tissue disease associated pulmonary arterial hypertension.

using the simplified Bernoulli equation.<sup>38</sup>

$$RVSP = 4v^2 + RAP$$

In the absence of any other anatomical abnormalities, the RVSP is equal to the pulmonary artery systolic pressure (PASP).<sup>38</sup> One should be aware of the limitations and inaccuracies of ECHO in estimating PASP, correlation of PASP on RHC may vary and a diagnosis of PAH should not be based on ECHO findings alone.<sup>39</sup>

Another ECHO parameter of use in the evaluation of PH is the tricuspid annular plane systolic excursion (TAPSE). The TAPSE represents the displacement of the tricuspid annulus toward the RV apex during systole and is closely correlated to RV function and can serve as a prognostic tool in PAH.<sup>40</sup> Finally, the presence of a pericardial effusion, right atrial dilatation, and septal displacement all portend a poor prognosis in PAH if present.<sup>41</sup>

### *Laboratory tests and serology*

All patients with suspected or confirmed PAH on RHC should undergo serological routine hematologic and biochemical analysis as well as testing for connective tissue diseases, HIV, chronic liver disease, and thyroid function. In patients with clinical examination findings suggestive of a connective tissue disease, antinuclear antibodies (ANA) and specific connective tissue disease autoantibodies can identify systemic sclerosis and other autoimmune conditions. In some cases, serological abnormalities may be the only manifestation in CTD-PAH. Thyroid abnormalities are prevalent among patients with PAH and should be tested for and treated.<sup>42</sup> Thyroid function testing should also be undertaken when there is deterioration in a previously stable patient. Liver function and hepatic function testing are necessary to identify chronic liver diseases and portopulmonary hypertension (PoPH) in newly diagnosed PAH. Liver enzymes may also be abnormal in the setting of congestive hepatopathy as a result of right heart failure, commonly with findings of mildly elevated serum bilirubin.<sup>43</sup> Patients with CTEPH should undergo thrombophilia testing.

Serum brain natriuretic peptide (BNP) is released from stretched cardiac myocytes and is elevated in the setting of right heart strain in PAH.<sup>44</sup> Serial monitoring of n-terminal pro-BNP (NT pro-BNP) levels can have prognostic value and be used to evaluate changes in right ventricular function in PH in response to treatment,<sup>45</sup> especially in patients who are not capable of performing the 6-min walk test due to muscle weakness.

Arterial blood gas measurements are useful in evaluating the degree of hypoxemia in patients with pulmonary hypertension. It can also be used to quantify the degree of left-to-right shunting when present.

### *Sleep study*

Sleep-disordered breathing has a high prevalence in the general population and all patients evaluated for PH should undergo screening for nocturnal hypoxemia and obstructive sleep apnea. Sleep apnea can result in mild elevation in pulmonary pressures that improve with the implementation of continuous positive airway pressure.<sup>46</sup>

### *6-Min walk distance*

The 6-min walk distance (6MWD) and degree of oxygen desaturation on exertion is a simple submaximal exercise method that determines functional capacity in patients with cardiopulmonary disease.<sup>47</sup> It is used to determine response to treatment and has an independent prognostic value. It is also used as an endpoint to demonstrate treatment efficacy in clinical trials.

### *Right heart catheterization and vasoreactivity testing*

The RHC is the gold standard test to diagnose and characterize PAH. The RHC testing to confirm the diagnosis of PAH and direct treatment decision should be performed at expert centers.<sup>48</sup>

Differentiating between HFpEF and PAH is diagnostically challenging. Findings of an elevated PAOP [a reflection of the left ventricle end-diastolic pressure (LVEDP)] on RHC can differentiate between the two conditions. However, in certain cases it may be necessary to perform an exercise or fluid challenge to unmask occult HFpEF; particularly when suspected in the setting of certain risk factors such as older age, enlarged left atrium, diabetes mellitus, systemic hypertension, and left ventricular hypertrophy.<sup>49</sup> In situations of elevated mPAP and concern for a co-existing pre-capillary PH in the setting of elevated PAOP ( $> 15$  mmHg), a low diastolic pulmonary gradient (DPG, the difference between the diastolic pulmonary artery pressure and the PAOP)  $\leq 7$  mmHg can help differentiate isolated post-capillary PH (Group 2 PH) from combined pulmonary hypertension with both a pre-capillary and post-capillary component (DPG  $> 7$  mmHg).<sup>50</sup>

All patients with IPAH, HPAH, or drug-induced PAH at time of RHC should undergo an acute vasoreactivity challenge with inhaled nitric oxide, unless contraindicated. Other alternative agents that may be used include intravenous (IV) epoprostenol, IV adenosine, or inhaled iloprost. A positive response is defined by a decrease in mPAP  $\geq 10$  mmHg below an absolute level  $\leq 40$  mmHg without a decrease in cardiac output.<sup>1</sup> Vasodilator testing may identify a small number of patients ( $< 10\%$  of IPAH cases) who may respond to high dose calcium channel blocker therapy.<sup>51</sup>

### *Ventilation–perfusion scan*

All patients diagnosed with PAH should undergo a lung ventilation–perfusion (V/Q) scintigraphy scan to evaluate for CTEPH. The V/Q scans have been demonstrated to have a higher sensitivity in detecting CTEPH in comparison to CT pulmonary angiography.<sup>52</sup> A normal or low probability V/Q essentially rules out CTEPH, whereas a high probability V/Q scan with perfusion defects is sensitive in detecting CTEPH (Image 5). Patients with a high probability V/Q scan should undergo pulmonary angiography and be referred to specialized centers for evaluation for pulmonary endarterectomy or balloon pulmonary angioplasty.<sup>53</sup>

### *Part 3: Treatment of PAH*

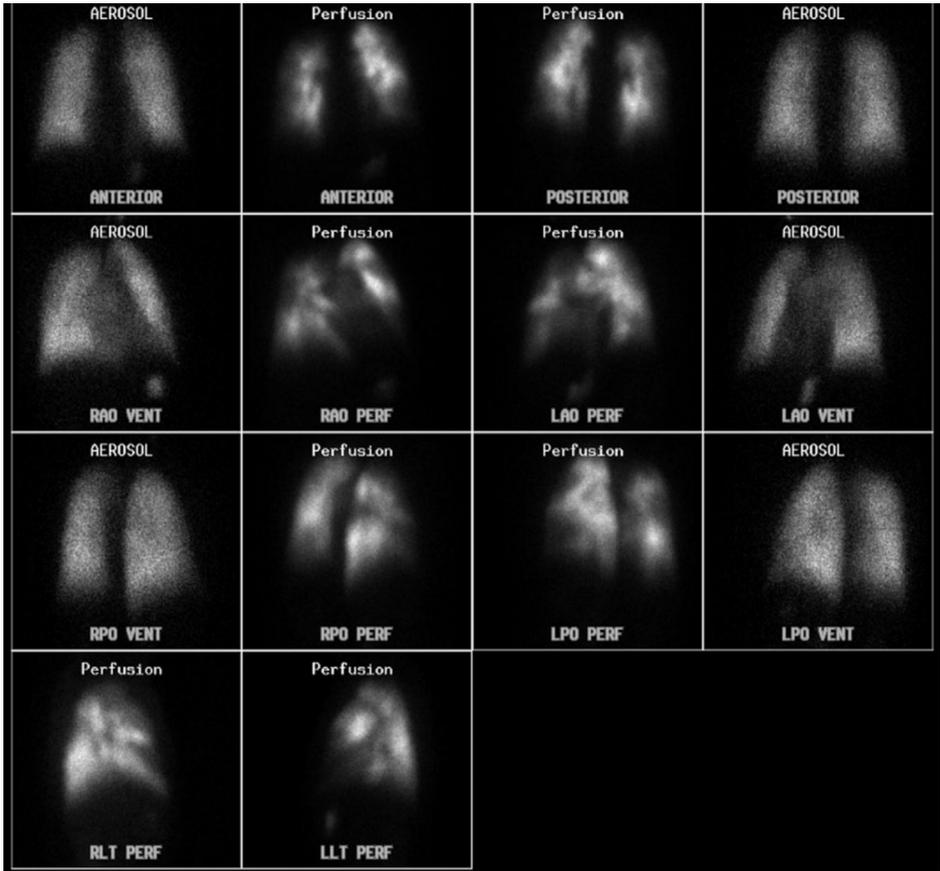
The goals of PAH treatment include alleviating patients symptoms, improving their functional status and quality of life, halting or reversing disease progression and including right ventricular dysfunction, and improving survival. The medical management of PAH involves two strategies; the first being supportive therapy directed at managing fluid status, hypoxemia, and right heart failure; the second is treatment with PAH specific drugs.

#### *Supportive therapy*

Adjunct nonspecific supportive therapy includes the use of oxygen, managing fluid status, anticoagulation, digoxin, and calcium-channel blockers. Despite limited controlled trials, expert opinion supports the use of these therapies and they continue to play a crucial role in the treatment of PAH patients.<sup>54,55</sup>

#### *Oxygen therapy*

PAH patients should be evaluated for hypoxemia and treated with supplemental oxygen therapy to maintain a partial pressure arterial oxygen ( $\text{PaO}_2$ )  $\geq 60$  mmHg. Hypoxia induced



**Image 5.** Ventilation–perfusion scan revealing multiple perfusion mismatches in a patient with CTEPH.

pulmonary vasoconstriction can worsen clinical status and the use of oxygen therapy can assist in reducing the PVR. The use of oxygen in the PAH population has been extrapolated from trials studying the use of oxygen in COPD patients.<sup>56</sup> It is recommended to initiate oxygen therapy for a  $\text{PaO}_2 \leq 55$  mmHg, or an oxygen saturation  $\leq 88\%$  at rest, with exertion, or during sleep.<sup>54</sup>

### Fluid management

Progressive pulmonary hypertension leading to right heart failure will subsequently result in fluid retention, lower extremity edema, ascites, and right to left ventricle interdependence.<sup>57</sup> The use of diuretics along with salt and water restriction can assist in managing the hypervolemic state, reduce right ventricle filling pressure, and improve symptoms. Loop diuretics, such as furosemide or bumetanide, are commonly used. The addition of the aldosterone receptor antagonist spironolactone may also proved long term benefit in PAH.<sup>58</sup> In severe cases of right heart failure, high doses of loop-diuretics with the addition of metolazone or even hospitalization for intravenous diuretic treatment may be required.<sup>55</sup>

Serum potassium levels should be monitored and managed carefully while on diuretics, especially in the setting of renal dysfunction or while receiving digoxin. Patients should be asked to check their blood pressure and measure their weight daily. Compliance with salt and fluid restriction should be reassessed with every visit. Peripheral edema may also occur as a side effect of PAH specific therapy, this is often managed with diuretic dose adjustment. In cases

where the PAH medication-associated edema does not respond to diuretics, leg elevation, and compression stockings can be utilized. In some cases switching to alternative PAH specific drug may be required.

### *Digoxin*

Digoxin is a cardiac glycoside that has observed benefit in treating congestive heart disease secondary to left heart failure. The short-term use of digoxin in patients with PH and right-sided heart failure has been shown to modestly increase the cardiac output,<sup>59</sup> while more recent studies indicate that long term use may also improve survival.<sup>60</sup> It can also be used in PAH patients with atrial arrhythmias. Currently, due to the limited randomized trials, its use in PAH remains controversial.

### *Anticoagulation*

The use of oral anticoagulation is recommended for patients with IPAH, HPAH, and drug associated PAH, however, supporting evidence is limited.<sup>54</sup> A recent study has shown survival benefit in IPAH<sup>61</sup>; however, in another study a survival advantage was not observed in patients' with IPAH and worse outcomes were detected used in patients with PAH secondary to systemic sclerosis.<sup>62</sup>

### *Calcium channel blockers*

A small number of PAH patients may show a response to acute vasoreactivity testing on RHC and may benefit from high dose calcium channel blocker (CCB) therapy.<sup>51</sup> Patients may be treated with nifedipine, diltiazem, or amlodipine and titrated to the goal dose (nifedipine 240 mg/day, diltiazem 720 mg/day, and amlodipine 10 mg/day in divided doses) or to the highest tolerated dose.<sup>63,64</sup> Diltiazem is favored for patients with a heart rate > 100 bpm, while nifedipine and amlodipine are favored in patients with a heart rate < 100 bpm. Empiric trial of CCB should not be given without performing acute vasoreactivity testing and is contraindicated in patients with severe right-sided heart failure and hypotension.<sup>65</sup> Verapamil should be avoided due to its strong negative inotropic activity.

### *PAH specific therapies*

Recent advances over the last two decades in understanding the pathogenesis of PAH has given rise to PAH specific treatments aimed at targeting three major molecular pathways: the prostacyclin pathway (i.e., prostacyclin analogues and prostacyclin receptor agonist), the nitric oxide pathway [i.e., phosphodiesterase type 5 inhibitors (PDE5i) and soluble guanylate cyclase stimulator], and the endothelin-1 pathway [e.g., endothelin receptor antagonists (ERAs)].

Patients with advanced PH, characterized by WHO functional class IV, high-risk hemodynamic findings (high RA pressures and low cardiac output), or high REVEAL risk score should be initiated on parenteral therapy while patients with less severe forms of PH may be first treated with oral agents.<sup>54,66</sup> Recently, data has shown that upfront or sequential combination therapy is associated with better outcomes compared to monotherapy treatment.<sup>67</sup> Finally, patients with progressive severe PAH despite medical therapy should be referred for lung or heart–lung transplant evaluation.

### *Prostacyclin analogues*

The prostacyclin analogues (epoprostenol, treprostinil, and iloprost) act via stimulating cyclic adenosine monophosphate (cAMP) mediated vascular smooth muscle relaxation resulting in pulmonary artery vasodilation.<sup>68</sup> The synthetic prostacyclin epoprostenol has been shown to

improve exercise capacity, functional class, and hemodynamics in patients with PAH.<sup>69</sup> Due to its short half-life, epoprostenol is administered parentally as a continuous infusion. More recently, inhaled and oral forms of the prostacyclin analogues have been made available allowing for an easier mode of administration for patients.

Selexipag is a novel prostacyclin receptor agonist that recently received FDA approval for the treatment of PAH. Treatment with selexipag has been associated with reduced time to death, clinical worsening, or PAH-related complications when used in combination with an ERA or PDE5i in comparison to placebo.<sup>70</sup>

### *Phosphodiesterase type 5 inhibitors*

The PDE5 inhibitors include two Food and Drug Administration (FDA) approved medications, sildenafil, and tadalafil. The PDE5 inhibitors exert their effects by inhibiting the enzyme phosphodiesterase type 5, leading to elevated cyclic guanosine monophosphate (cGMP) and pulmonary vasodilation. PDE5i have been shown to improve exercise capacity, functional class, and delay time to clinical worsening.<sup>71,72</sup> The use of concurrent nitrates is contraindicated due to risk of hypotension.

### *Soluble guanylate cyclase stimulator*

Riociguat is newer class of drug, a soluble guanylate cyclase stimulator, indicated for treating inoperable or persistent/recurrent post operative CTEPH.<sup>73</sup> It has been shown to improve exercise capacity, functional class, as well as time to clinical worsening in PAH patients.<sup>74</sup> Riociguat acts synergistically with endogenous nitric oxide and also by directly stimulating soluble guanylate cyclase independent of nitric oxide. The use of concomitant nitrates or PDE5i is contraindicated due to the risk of hypotension.

### *Endothelin receptor antagonists*

The endothelin receptor antagonists (ERA) block binding of endothelin-1 to the endothelin receptors (ET<sub>A</sub> and ET<sub>B</sub>). There are currently three FDA approved ERAs; bosentan, ambrisentan, and macitentan. ERAs have been shown to improve hemodynamics and exercise capacity, as well as prevent clinical worsening of PAH.<sup>75,76</sup> Bosentan carries a risk of hepatotoxicity and as such liver function should be monitored every month. All ERAs carry a risk of major birth defects if used by pregnant females, as such all females of childbearing age should undergo monthly pregnancy tests.

## **Part 4: PAH-associated conditions**

### *Drug and toxin induced PAH*

Much of the initial interest and attention on drug-induced PAH focused around the use of potent appetite suppressants (anorexigens), such as aminorex fumarate in 1965 subsequently leading to its discontinuation.<sup>77</sup> Today, drug and toxin-induced PAH comprise a relatively small proportion of PAH patients. The recent 2013 Nice guidelines identified specific medications as risk factors for developing PAH and categorized based on the strength of data available (Table 3).<sup>3</sup> Aminorex fumarate, fenfluramines, dexfenfluramine, benfluorex, and toxic rapeseed oil were all designated as definite risk factors for the development of PAH. The use of selective serotonin receptor inhibitors (SSRI) has been associated with the development of PPHN, especially when taken after 20 weeks gestation. Outside of pregnancy SSRI are not considered to be a risk factor for PAH.<sup>78</sup>

Several medications have been classified as a possible linked to developing PAH, including dasatinib, St. John's Wort, interferons (INF), and cocaine. A review of the French registry has identified a small proportion of patients receiving dasatinib, a BCR/ABL kinase inhibitor used in the treatment of chronic myelogenous leukemia, that developed PAH.<sup>79</sup> While the proportion of patients treated with dasatinib was relatively small, of those who developed PAH, the hemodynamic effects were not completely reversible after discontinuing the drug. The use of type 1 IFN, IFN- $\alpha$  in patients with hepatitis C and IFN- $\beta$  in individuals with multiple sclerosis have also been associated with the development of PAH, possibly linked to endothelial dysfunction induced by the drugs.<sup>80,81</sup>

Amphetamines, methamphetamines, and L-tryptophan (a dietary supplement) have been classified as a likely risk factor for developing PAH. Stimulants have been suspected to have an association with PH and one retrospective study found that patients with idiopathic PAH were 10 times more likely to have used amphetamines, methamphetamines, cocaine or a combination compared to patients with PAH and known risk factors.<sup>82</sup> Based on this, the guidelines identify stimulants as a likely risk factor and highlight fenteramine, topiramate, methylphenidate, ropinerole, and mizindol as other medications with similar mechanisms of action that they feel warrant close monitoring for development of PAH for presumed theoretical risk.<sup>3</sup> The use of certain drugs and alkylating agents, such as mitomycin-C, BCNU, cyclophosphamide, bleomycin have been closely associated with developing PVOD.<sup>83</sup> To date, there has been no evidence linking smoking tobacco, and the use of oral contraceptives and estrogen to PAH.

Despite the wide use of these various medications, drug and toxin induced PAH remains a rare entity. An explanation is that these drugs serve as a trigger for developing PAH in susceptible patients. Identifying these at risk patients remains an area of active research.

#### *Connective tissue disease-associated pulmonary arterial hypertension*

PAH can be associated with various autoimmune and connective tissue diseases particularly scleroderma (SSc), as well as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), Sjogren's syndrome, antisynthetase syndrome, dermatomyositis, and polymyositis. While CTD-associated PAH (CTD-PAH) are very similar in pathogenesis and hemodynamic profile to IPAH, prognosis in CTD-PAH is far worse compared to IPAH despite modern therapies and is one of the leading causes of mortality in this population.<sup>84</sup> SSc-PAH carries the worst prognosis among the CTD; with patients that have SSc respiratory disease-associated PH having a poorer survival compared to isolated SSc-PAH.<sup>84</sup> As such, it is important to screen for underlying CTD during the evaluation of patients with PH.

Approximately 8–14% of patients with SSc develop PAH based on RHC measurements.<sup>85</sup> Assessments based on ECHO in SSc tend to overestimate the prevalence of PAH.<sup>86</sup> The exact prevalence of PAH in other CTD has not been well characterized, but is believed to be lower in SLE affecting 0.5–14% of patients,<sup>87</sup> and as high as 50% in MCTD.<sup>88</sup>

In the evaluation of PAH, autoantibody serology assessment can identify the underlying CTD and includes testing for ANA, anti-DNA in SLE, anti-centromere and anti-Scl-70 in SSc, antisynthetase antibodies (anti-Jo, anti-PL-12, anti-PL-7, etc.) in dermatomyositis and polymyositis, anti-Ro and anti-La in Sjogrens, and anti-U1-RNP in MCTD.

All patients diagnosed with SSc should have a baseline evaluation with a clinical examination, PFTs, and ECHO. The use of 6MWD may be affected by underlying musculoskeletal involvement in SSc. Risk factors such as advanced age, scleroderma disease duration, an isolated reduction in DLCO, an FVC%/DLCO% ratio < 1.6, and the degree of telangiectasia have all been positively linked to risk of developing PAH in SSc.<sup>89,90</sup> Limited cutaneous scleroderma (CREST) is more likely to be associated with PAH than systemic sclerosis,<sup>91</sup> as such, presence of anti-centrosome is more positively associated with development of PAH than anti-SCL-70. Previous screening recommendations was based on consensus and largely centered on symptoms in addition to echocardiogram findings. The DETECT study identified several key discriminatory variables which they used to construct a two part algorithm for identifying patients who should undergo a

RHC. The algorithm provides increased sensitivity and would ideally allow for earlier detection and treatment and improve mortality.<sup>92</sup> It is important to evaluate for other causes of PH in this population that may include PH secondary to interstitial lung disease, heart disease, and PVOD.

Combination therapy with PAH-specific drugs (prostacyclins, PDE5i, and ERA) is used in the management of CTD-PAH, however, patients in this population have been observed to have a lower response to PAH-specific therapy compared to IPAH.<sup>54</sup>

### *Congenital heart disease-associated pulmonary arterial hypertension*

Congenital heart disease-associated PAH (CHD-PAH) refers to the development of PAH in the setting of a congenital heart defect. There are multiple defects known to be associated with PAH, each with its own unique impact on normal cardiac function resulting in the development of PAH. Improved identification and management of various CHD has allowed patients to survive into adulthood but a small portion can go on to develop PAH. As our understanding of both congenital heart disease and pulmonary hypertension has grown so has our understanding of how to manage this unique population, which is reflected in the updated Nice classification categorizing CHD-PAH as Group 1-associated diseases.<sup>3</sup>

The broad category of congenital heart disease refers to a complex heterogeneous group of defects, of which only a few are associated with PAH. Defects associated with left-to-right shunting such as atrial septal defects (ASD), ventricular septal defects (VSD), and patent ductus arteriosus (PDA) are the usual defects observed in CHD-PAH. The left-to-right shunting is the basic mechanism that drives changes in the pulmonary vasculature resembling that of PAH, which is why ASD, VSD, and PDA-associated PAH were classified as a Group 1-associated disease.

PAH in this population is believed to develop as a maladaptive response to the left-to-right shunting resulting in vascular changes similar to IPAH. The left heart and systemic circulation is a high pressure, high resistance circuit compared to the right side. The pressure and resistance difference allows for shunting resulting in volume and pressure overload of the pulmonary vasculature. This in turn leads to endothelial damage, smooth muscle hyperplasia, fibroblast activation, platelet activation, and thrombosis. Other changes such as imbalance of vasodilators to vasoconstrictors are also seen. As these changes occur and the right-sided pressures rise, this can ultimately result in Eisenmenger's syndrome, which refers to shunt reversal and resultant systemic hypoxemia depending on the degree of shunting.

The location and size of the defect ultimately determine the likelihood of developing PAH. It is estimated that only 5–10% of patients with these defects will go on to develop PAH.<sup>93</sup> VSD are the most common CHD and most likely to cause PAH as both ventricles will contribute to the pulmonary blood flow.<sup>94</sup> Small lesions can intrinsically restrict shunting therefore size of the lesion is crucial for identifying at risk patients. Unlike VSDs, ASDs allow for shunting during diastole due to the increased compliance of the right heart. The right ventricle will hypertrophy in response to the increased volume, which will cause a reciprocal drop in compliance, limiting further shunting and chance of developing PAH.<sup>95</sup> PDA shunt during the entire cardiac cycle and degree of shunting is directly related to the size of the defect.

Presenting signs and symptoms are similar to that of other PAH patients with some notable exceptions. Typically patients will report dyspnea on exertion and fatigue as initial symptoms. As PAH worsens, patients can also experience chest pain, syncope and hemoptysis. On examination, murmurs may be detected depending on location of the defect, as well as central cyanosis, clubbing, right ventricular heave, JVP, and lower extremity edema. VSD murmurs will occur during systole while arterial murmurs are continuous. It is important to note that these patients are at risk for developing endocarditis, and new or changing murmurs in the right clinical context may reflect this.

Testing is usually significant for decreased exercise tolerance. Blood work may show a secondary erythrocytosis. CXR typically will not show pruning, which can be seen in other forms of PAH, but may reveal right atrial and ventricular enlargement. ECG may demonstrate right atrial enlargement including P-pulmonale, while ECHO can demonstrate the level and size of the

defect as well as pressure gradients. Defects not well characterized on ECHO can be better visualized with Cardiac CT or MRI.

Patients with CHD in whom there is concern for developing PAH should undergo echocardiography and if indicated, RHC to establish the diagnosis. These patients are best served by being evaluated and treated in centers that are familiar in managing patients with CHDs as well as PAH. Many of the same advanced therapies are used though there is a paucity of high quality evidence guiding treatment.

Given the unique physiology, there are several notable considerations and exceptions that differentiate treatment of PAH in this population with other Group 1 disorders. The connection between the right and left heart places these patients at higher risk for paradoxical embolization and stroke. This communication also classifies these patients at high risk for infective endocarditis, requiring them to receive prophylactic antibiotics.<sup>96</sup> Interestingly calcium channel blockers are avoided in this population, while anticoagulation is controversial given lack of improvement in mortality and the risk of pulmonary hemorrhage and hemoptysis. Pregnancy should be avoided as it poses a threat to both the mother and fetus. Women should be placed on a contraceptive method due to the life-threatening nature of pregnancy in PAH. Finally, these patients are at risk of hyperviscosity and iron deficiency secondary to the erythrocytosis.

Surgical treatment options are available but the expected morbidity and mortality associated with the surgery are worse compared to the natural course of the disease. It is for this reason that shunt closure and transplant are only considered in a small portion of patients. Criteria have been proposed for whom closure should be considered but the decision is complex and must consider the patient's age, defect, and hemodynamics measured on right heart catheterization. Patients with small defects or Eisenmenger's syndrome are not typically considered for closure. These patients typically survive multiple decades, which some attribute to long standing nature of the defect allowing for slow adaptation.<sup>97</sup> As well, in the case of Eisenmenger's syndrome, cardiac output to the pulmonary system is limited at the expense of central cyanosis and hypoxemia reducing progression. For these reasons, transplants are typically reserved for highly symptomatic patients despite optimal medical therapy.

### *Portopulmonary hypertension*

Portopulmonary hypertension (PoPH) describes pulmonary arterial hypertension that develops in a patient with portal hypertension. The vast majority of cases are due to cirrhosis, however other causes of portal hypertension have also been associated with PAH.<sup>98</sup> It is important to recognize that PoPH is a separate entity from hepatopulmonary syndrome. While the two can share similar symptoms, hepatopulmonary syndrome describes hypoxemia that develops due to extensive shunting, where as PoPH is characterized by pulmonary vascular hemodynamics and remodeling characteristic of Group 1 PH that does not typically result in hypoxemia short of severe disease.

PoPH is relatively uncommon even among patients with portal hypertension. The prevalence ranges between less than 1% and up to 6% depending on the population studied. The incidence was highest in patients undergoing evaluation for liver transplant.<sup>99–101</sup>

There are several theories regarding the etiology, though increased levels of vasoconstrictors are felt to contribute most to the pathogenesis. Serotonin and endothelin-1 are two vasoactive neurohormones of many garnering significant attention. Higher circulating levels of serotonin, predominantly produced by enterochromaffin cells, results from decreased degradation by the liver and fewer circulating platelets which are able to uptake and store serotonin.<sup>102</sup> Endothelin-1 has also been demonstrated to be higher in cirrhotic patients.<sup>103</sup> A less likely etiology involves thromboembolism from the portal to pulmonary system; however, studies suggest that thrombosis is more likely to be the result of in situ formation rather than embolism.<sup>104,105</sup>

Patients will typically have known cirrhosis but may report a history such as alcohol abuse, infectious hepatitis risk factors like drug abuse or prior blood transfusions, or non-cirrhotic conditions such as Budd-Chiari or portal vein thrombosis. On physical exam, patients will show

stigmata of portal hypertension or cirrhosis. Ascites, jaundice, caput medusa, spider angiomas, palmar erythema can be seen in addition to evidence of pulmonary hypertension, such as loud P2, elevated JVP, right ventricular heave, and pedal edema.

When PoPH is suspected in a patient with portal hypertension, work-up should include echocardiography as well as workup to exclude other causes of PAH. Patients with elevated RVSP as well as patients being considered for liver transplant should undergo right heart catheterization. Careful analysis of the RHC data in this population should be undertaken to differentiate PAH from pulmonary hypertension as a result of passive congestion (secondary to fluid overload or HFpEF) or a high cardiac output state.

Once PoPH has been identified, patients should be treated at pulmonary hypertension centers. Initial therapies should be directed at optimizing treatment of underlying disease. Diuretics and supplemental oxygen (if hypoxemic) are standard of care and those who have persistent WHO FC II-IV symptoms despite optimization are candidates for advanced therapies. Beta-blockers and TIPS are typically avoided since beta-blockers have been shown to decrease cardiac output and exercise tolerance while TIPS has been associated with an immediate worsening of RAP, mPAP and PVR.<sup>106,107</sup>

Liver transplantation is the definitive treatment for cirrhosis, however several important factors must be considered in patients with PoPH. First, while PoPH is not necessarily an indication for liver transplant, it is one of the conditions that can qualify for MELD exception points, in order to more accurately reflect the patient's increased risk of mortality and need for liver transplant. Second, severe PoPH (mPAP  $\geq$  50) has an unacceptably high perioperative and postoperative mortality and so the committee must consider the patient's individual hemodynamic profile. In one series, liver transplant with severe PAH had 100% mortality while PAH with mPAP  $<$  35 mmHg was not associated with a significantly increased mortality compared to non-PAH patients.<sup>108</sup> These patients should have PAH therapies and by extension their vascular profile optimized to reduce their expected mortality in order to qualify and benefit from liver transplantation.

Outcomes are typically worse when compared to patients with IPAH. A review of the REVEAL registry showed a 2-year survival of 67% vs. 85% in patients with PoPH compared to IPAH, and a 5-year survival of 40% vs. 64%.<sup>109</sup> Prognosis was better in patients who did not have cirrhosis or compromised cardiac function.<sup>110</sup>

### *HIV-associated pulmonary arterial hypertension*

As treatment strategies for HIV improved, so has survival rates, which in turn, has allowed us to identify secondary conditions associated with HIV. PAH-associated HIV is one such disease with the earliest reports published in the late 1980s.<sup>111</sup> Histologic pulmonary vascular changes are very similar to those seen in PAH prompting HIV-associated PAH (HIV-PAH) to be classified as a Group 1-associated disorder in the Nice classification. Despite the significant advances in HIV treatment, the incidence of HIV-PAH has remained stable over the past several decades but with optimal treatment, survival is similar to IPAH.<sup>112</sup>

As compared to other PAH-associated diseases, the body of research available is much more limited. This is in part due to the fact HIV-PAH prevalence is relatively low, estimated about 0.5% of HIV infected patients. As well, HIV infection can be associated with several confounding variables including cocaine use, intravenous drug use, and co-infection with Hepatitis B and C.<sup>112</sup> This can make it hard to interpret some of the early studies as well as isolating ideal study candidates for future investigations. Of the available literature, the reported time to development PAH ranges from roughly 1.5 to 10 years.<sup>112,113</sup>

HIV-PAH is suspected to develop through a combination of host and viral factors. The most notable HIV-associated proteins garnering attention include gp120, TAT, and NEF. Gp120 a surface protein has been shown to increase endothelin-1 secretion by circulating monocytes, while TAT, a transactivator needed for HIV viral replication, can down-regulate expression of BMPR2.<sup>114,115</sup> NEF is an adaptor protein that has been demonstrated in multiple studies to be

associated with the development of the plexiform lesions of pulmonary vasculature characteristic of idiopathic PAH.<sup>116,117</sup>

Presenting symptoms and signs are largely similar to other PAH-associated diseases. Dyspnea on exertion and fatigue are typically the earliest symptoms and as disease progresses, patients can complain of lower leg swelling, hemoptysis, light-headedness, and syncope. On examination, elevated JVP, right ventricular heave, pedal edema can be seen depending on the severity. If the HIV is untreated patients can have a history of recurrent atypical infections or even stigmata of AIDS.

While asymptomatic HIV patients should not be screened for PAH, development of dyspnea and fatigue should prompt workup with ECHO and subsequent RHC if the ECHO is suggestive of PAH. Other causes of PAH that should be evaluated for and ruled out include left heart disease, CTD, liver disease, and CTEPH. Viral load and CD4 count should be obtained as both can demonstrate treatment compliance and provide prognostic information. Vasodilator testing is typically not performed during catheterization because these patients are unlikely to have a response.

Patients should be treated at centers familiar with both PAH and HIV. Many of the same treatment strategies for other PAH etiologies are also used for HIV-PAH with a few important exceptions. Calcium channel blockers are not used due to the previously mentioned lack of vasodilator response and risk of hypotension. Anticoagulation is also not recommended due to risk of hemoptysis, as well as potential drug interactions, and compliance issues.<sup>118</sup> With respect to advanced treatments, research is limited; however epoprostenol, bosentan, and sildenafil have all been studied and show improvement in 6MWD as well as hemodynamics but more research is needed comparing different prostacyclins, ERAs, and PDE5i. Of note, sildenafil can interact with certain HAART medications and should be avoided, underscoring the importance of careful coordination between PAH and HIV treatment specialists when choosing a pharmacotherapy regimen.

In addition to PAH treatment, all patients with HIV-PAH should be treated with HAART therapy. The HAART therapy, without PAH therapies, was associated with significantly worse outcomes.<sup>119</sup> Overall survival at 1 and 3 years is reportedly 73% and 47%, respectively, with improved survival noted in patients with lower NYHA class (I and II). A CD4 count greater than 212 cells/mm<sup>3</sup> and a cardiac index greater than 2.8 L/min/m<sup>2</sup> are additional predictors of improved survival independent of NYHA class.

### *Schistosomiasis-associated pulmonary arterial hypertension*

Worldwide, schistosomiasis is the most common cause of PAH although it is rarely encountered in developed nations. Schistosomiasis is a disease with multiple manifestations caused by a parasitic blood fluke. The hepatosplenic form of the disease is marked by liver fibrosis and the subsequent pathologic changes allows for a small portion of the population to go on to develop pulmonary vascular changes similar to that of PAH termed schistosomiasis-associated PAH (SaPAH). Despite its global impact and prevalence, the body of evidence behind diagnosis and management of SaPAH is limited even compared to other more rare causes of PAH, likely related to the epidemiology of the disease.

Schistosomiasis is endemic to Africa, but is also seen East Asia, the Middle East, and South America. Three species of schistosome (*Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma hematobium*) are responsible for the majority of cases of schistosomiasis in humans, and the distributions as well as disease manifestations vary slightly between species. *Schistosoma mansoni* is largely found in Africa and South America, while *S. japonicum* is predominantly East Asia. Both *S. mansoni* and *S. japonicum* affect the gastrointestinal vascular system while *S. hematobium*, typically found in Africa and the Middle East affects the genitourinary vasculature. Worldwide prevalence is estimated to be around 200 million people. Of these, about 7% have developed pulmonary hypertension related to their disease.<sup>2</sup>

SaPAH is thought to develop after the eggs inside a chronically infected host embolize to the lungs through portosystemic shunts. Initial infection starts with mature schistosome larvae

directly penetrating through skin that it comes into contact contaminated fresh water. These larvae will travel to the liver and mature releasing adult forms, which migrate to specific locations where they will produce eggs to be released. *S. mansoni* and *S. japonicum* infect the mesenteric veins while hematobium migrates to the venous plexus of the bladder. Eggs are made and released, most of which penetrate through the vasculature and out into their respective excrement, stool, or urine. Some, however, may embolize to the liver causing periportal granulomas and fibrosis eventually resulting in cirrhosis. As cirrhosis worsens, systemic shunts form allowing for egg embolization to the systemic circulation and subsequently the pulmonary vasculature. In the lungs, similar granulomas form, however, instead of fibrosis, the pathologic plexiform lesions of PAH develop.

Clinical manifestations and diagnosis of SaPAH are essentially the same as idiopathic PAH with some important notes.<sup>2</sup> Dyspnea, fatigue are common and depending on severity signs and symptoms of right heart failure can also be seen.<sup>120</sup> Unlike other forms of PAH, SaPAH can show a fine miliary pattern on chest imaging. Schistosomal infection can be detected with microscopy of stool or urine for eggs, as well as serology for antibodies or antigens. Diagnosis is typically accepted when there is clinical and laboratory evidence of schistosomiasis as well as evidence of elevated pulmonary pressures on RHC. Formal diagnostic guidelines have not been established but have been proposed.<sup>121</sup>

Guidelines regarding treatment are founded on similarly sparse evidence and formal guidelines have not been published. Praziquantel is the primary treatment of choice for the underlying infection and there is some evidence to suggest that it may reverse some of the vascular changes in the lung.<sup>122</sup> Vasoreactivity testing is typically negative, therefore, calcium channel blockers are not recommended.<sup>123</sup> Anticoagulation and TIPS are not recommended due to bleeding risk and volume overload, similar to PoPH.<sup>124</sup>

There is even less evidence behind advanced PAH therapies. A small recent study demonstrated improvement in both symptoms and hemodynamics with PDE5i as well as ERAs in this population; however, rigorous testing comparing treatment effect between the various PAH-specific drugs is lacking. Given the pathologic similarities with PoPH, it has been suggested that data from PoPH studies can be extrapolated to be applied to SaPAH.<sup>121</sup>

## Conclusion

Pulmonary arterial hypertension is a progressive and debilitating disease that requires early recognition and treatment. PAH can be idiopathic, heritable, or associated with various drugs or conditions, all of which share a similar pathophysiology. Recognizing the clinical manifestations of PAH and being able to distinguish patients with PAH from other groups of pulmonary hypertension can be challenging, but once detected can allow for early administration of PAH-specific therapy and improved outcomes.

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