Diagnostic Assessment of the Pulmonary Hypertension Patient

Bradley M. Wertheim, MD
Division of Pulmonary and Critical Care Medicine
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA

Bradley A. Maron, MD
Division of Cardiovascular Medicine, Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
Department of Cardiology, Boston VA Healthcare System
Boston, MA

DEFINING PULMONARY HYPERTENSION
Based largely on historical data, the definition of pulmonary hypertension (PH) requires a mean pulmonary artery pressure (mPAP) ≥25 mm Hg measured supine, at rest by cardiac catheterization. The relevance of this criterion to adverse outcome has since been reproduced in numerous patient populations, providing outcome-linked data on the importance of elevated pulmonary artery pressure to clinical risk. However, mPAP is a continuous variable and data from recent epidemiological reports and prospective studies have shown an increase in hard clinical events at mPAP levels beginning around 19 mm Hg. Although these data appear to challenge the traditional PH criterion of mPAP ≥25 mm Hg, the relevance of these findings to daily clinical practice is not resolved currently.

CLASSIFYING PH: THE WHO DIAGNOSTIC CLASSIFICATION GROUPS
Patients meeting the hemodynamic definition of PH may be categorized further into one of 5 World Health Organization (WHO) diagnostic classification groups. Generally, patients are classified as Group 1 if PH is idiopathic, hereditary, occurs in the setting of systemic sclerosis or portal hypertension, or, more generally, is in the absence of primary lung, cardiac, or thromboembolic disease. However, the following additional hemodynamic criteria must also be met: pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and pulmonary vascular resistance (PVR) >3.0 Wood units. These patients are diagnosed with pulmonary arterial hypertension (PAH) (ie, WHO Group 1 PH), which is due to a complex pulmonary arteriopathy characterized by concentric hypertrophic remodeling, plexogenic lesions, vascular fibrosis, and microthrombosis. Most commonly, PAH is idiopathic but may also be due to heritable causes, particularly germline mutations in the gene encoding bone morphogenetic protein receptor-2 (BMPR2) protein. Patients may also have PAH in the setting of systemic sclerosis (or other connective tissue disease), human immunodeficiency virus (HIV), portopulmonary hypertension, and congenital heart disease due to uncorrected shunt. Schistosomiasis is the most common cause of PAH worldwide, although encountered rarely in industrialized nations. Pulmonary veno-occlusive PH is classified as a form of PAH that may be genetic, and results in luminal obliteration to pulmonary veins.

Patients with PH in association with primary lung or left heart disease are classified as Group 2 or 3, respectively, although overlap between these diseases is common in clinical practice. Chronic thromboembolic pulmonary hypertension (CTEPH) describes a distinct clinical pathophenotype that involves in situ thromboembolic remodeling of distal pulmonary arterioles corresponding to a distinct clinical and radiographic pattern (see below), and is classified as Group 4. Patients with well-established but uncommon causes of PH, such as sarcoid or fibrosing mediastinitis, are classified as Group 5 or “miscellaneous,” as unified treatment strategies for generally affected patients are not available.

HISTORY AND PHYSICAL EXAMINATION
Diagnosing PH and ultimately determining the appropriate classification often requires extensive diagnostic testing, but useful clues can be gathered from a skilled history and physical examination. It is notable that up to 70% of the pulmonary vasculature may be remodeled prior to clinical presentation in some PH patients, particularly PAH. This may be due, in part, to early symptoms.
that are generally nonspecific, such as dyspnea and fatigue, and as a result are often attributed to other cardiopulmonary disorders.\(^{18}\) Thus, overall, the first step toward diagnosing PH in clinical practice is a high index of clinical suspicion. Other PH symptoms include “bendopnea” (dyspnea provoked by bending), weight gain (suggestive of volume overload and right heart failure), exercise intolerance, and in severe disease presyncope, syncope, or chest pain.

Once PH is suspected, the focus of the history is on characterizing symptoms, clinical trajectory, symptom burden, and functional class, which can be informative on disease severity. Clinicians should screen patients for risk factors that may predispose to a particular PH subphenotype, such as tobacco, methamphetamine, or alcohol use, other classical risk factors for diseases that affect lung or cardiac function, or circumstances that raise the specter of prior or recent venothromboembolic disease (eg, deep vein thrombosis or pulmonary embolism).\(^{19}\) Clinicians must also be mindful of specific diseases that associate with PAH, including systemic sclerosis and less commonly other connective tissue diseases, as well as HIV or hepatic cirrhosis. Importantly, PH under diagnosis is common in populations with limited access to health care.\(^{20}\) A family history of PAH should be considered seriously, since this may inform a diagnosis of heritable PAH due to a mutation in the BMPR2 gene among other less common monogenetic risk factors for pulmonary vascular disease.\(^{21}\)

A “PH-focused” physical examination does not really exist, since determining the etiology of PH must include a detailed assessment of all organ systems. Nonetheless, emphasis should be placed on assessing potential consequences of PH on heart sounds, jugular venous pressure, hepatosplenic congestion, gut or lower-extremity edema, and peripheral perfusion, which are critical for staging this disease and can have immediate ramifications on prognosis, treatment selection, or patient disposition. Generally, severe PH is associated with a loud or paradoxical split S2, which is due to the accentuating effect of right ventricular (RV) afterload on pulmonic valve closure, while increased RV pressure may manifest by appreciating right-sided S3 heart sounds, RV lift, or increased jugular venous pressure. Particularly worrisome are findings indicative of cardiogenic shock due to cor pulmonale; in this situation, a change in mental status, severe fatigue, severely decreased functional class, and systemic hypotension in the setting of cool and edematous lower extremities may be a medical emergency requiring immediate hospitalization.

**INITIAL TESTING**

In the ambulatory setting, patients suspected of PH should undergo electrocardiography (ECG), chest x-ray, and comprehensive biochemical monitoring to assess renal function and liver function (Table 1). Selecting patients to assess connective tissue disease serology, hepatitis, or HIV status hinges on pretest probability, which, in turn, is dictated by the patient’s overall clinical profile and examination findings. For example, patients with known ischemic cardiomyopathy without extracardiac symptoms may not require full immunological and serological assessment, since false-positive results for systemic sclerosis and other systemic disorders have been reported.\(^{22}\) Nonetheless, a low threshold to include assessment for these diseases as well as CTEPH (see

| Diagnostic Tests                                      | Clinical Yield                                                                 |
|------------------------------------------------------|-------------------------------------------------------------------------------|
| **Office evaluation**                                |                                                                               |
| History                                              | Index of suspicion for PH                                                     |
| Physical Examination                                 |                                                                               |
| CXR                                                  |                                                                               |
| ECG                                                  |                                                                               |
| **Directed laboratory testing and history**           |                                                                               |
| Cardiac structure and function:                     |                                                                               |
| Transthoracic echocardiogram                         |                                                                               |
| If indicated: TEE, cMRI                              | Cardiac chamber size and morphology                                          |
| **Pulmonary function**                               |                                                                               |
| PFT/ABG                                              | Cardiac mechanical function                                                  |
| Overnight oximetry                                   | Gas exchange                                                                  |
| Polysomnography                                      | Sleep-disordered breathing                                                   |
| **Chest imaging**                                    |                                                                               |
| V/Q scan                                             | PE/CTEP                                                                       |
| Chest CT/CTA                                         | Parenchymal lung disease                                                      |
| **Right heart catheterization**                      |                                                                               |
| If indicated: Provocative maneuvers                   | Anatomic considerations                                                       |
| Vasoreactivity testing                               |                                                                               |
| Left heart catheterization                           | Confirm PH diagnosis                                                          |
| **Exercise testing**                                 |                                                                               |
| 6-minute walk                                        | Hemodynamic profile                                                          |
| CPET                                                 | Risk stratification                                                           |
|                                                      | Track response to therapy                                                     |

**Table 1. Diagnostic evaluation of pulmonary hypertension. Abbreviations:** AcT, acceleration time; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTA, computed tomography angiography; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest radiography; ECG, electrocardiogram; HIV, human immunodeficiency virus; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PH, pulmonary hypertension; RVOT, right ventricular outflow tract; TEE, transesophageal echocardiogram; V/Q, ventilation-perfusion scintigraphy.\(^{26}\)
below) in the diagnostic evaluation of PH is warranted in patients for whom a cause of PH is unclear, since identifying the underlying cause of pulmonary vascular disease is associated with variable prognosis and treatment recommendations. Limited systemic sclerosis, which is the most common subtype to afflict the pulmonary circulation, can be associated with an abnormal immunological profile, including elevation in levels of anti-centromere, double-stranded (ds) DNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP (Table 2). Interpreting these data may require consultation with a rheumatologist or other connective tissue disease clinical specialist.

Some clinicians will also utilize N-terminal pro-brain natriuretic peptide (NT-proBNP) or troponin level as part of the diagnostic (and risk stratification) approach to PH, although these assays are not specific to PH and can be increased in patients due to a separate, predominant pathophenotype (eg, myocardial infarction, isolated left heart failure, pulmonary embolism, others). Overall, the initial point of care testing is intended to provide clues on the diagnosis of PH, such as central vascular congestion or RV hypertrophy on chest x-ray and ECG, respectively, as well as staging patients by virtue of physical examination of biochemical assessment. Still, the diagnostic evaluation of PH requires more detailed information.

### 2-DIMENSIONAL ECHOCARDIOGRAPHY

Transthoracic 2-dimensional echocardiography is an important tool to assess RV geometry, systolic function, systemic venous congestion, and estimated pulmonary artery systolic pressure (PASP). Since echocardiography is noninvasive, it is often the first quantitative diagnostic test for PH. Importantly, the accuracy of echocardiography for measuring PASP hinges on adequate Doppler interrogation of a tricuspid regurgitant jet, which may be absent in some patients with PH or can be difficult to assess in patients with poor acoustic windows due to large body habitus, chronic obstructive pulmonary disease (COPD), or other common comorbidities. Indeed, data from population studies suggest only modest correlation between PASP estimated by echocardiography and measured directly using the gold standard test, cardiac catheterization, even when both tests are performed on the same day. Additionally, the accuracy of echocardiography is limited further in patients for whom pulmonary artery pressure is abnormal, but increased only mildly. Owing to increased adverse clinical outcome associated with even subtle elevations in mPAP, this is an important consideration when interpreting echocardiography study results.

Despite these limitations with respect to PASP measurements, some key data can be acquired from echocardiography that are useful in diagnosing and staging PH. For example, RV cavity dilation, impaired RV systolic function (eg, decreased tricuspid annular plane of systolic excursion [TAPSE] <1.5 cm), hepatic vein dilation or blunted respirophasic dilation, and pericardial effusion provide anatomical or functional information on right heart pathophysiology. Although cardiac output (CO) and PAWP cannot be measured accurately by echocardiography, algorithms have been proposed that integrate multiple variables as a method to identify patients for whom an increase in PVR is likely. For example, the presence of a “notch” in the Doppler envelope of the RV outflow tract and decreased pulmonary artery acceleration time in the setting of a normal left atrial dimension have been shown to correspond to PVR >3.0 Wood units in

| Antigen                  | Approximate Frequency in SSc | Clinical Relevance                                                                 |
|-------------------------|-------------------------------|-------------------------------------------------------------------------------------|
| Anti-centromere         | 16%-39%                       | lcSSc > dcSSc Highly specific for SSc; also suggests increased risk of developing SSc in those with isolated Raynaud phenomenon Most commonly observed autoantibody in SSC-PAH Pulmonary fibrosis and renal crisis uncommon |
| Anti-topoisomerase I (Scl-70) | 9%-39%                       | dcSSc > lcSSc Associated with pulmonary fibrosis and digital ulcers Higher mortality Serum levels may correlate with disease activity |
| Anti-RNA polymerase III | 4%-25%                        | dcSSc Highly specific for SSc Associated with scleroderma renal crisis and malignancy |
| Anti-TH/To              | 1%-7%                         | lcSSc Associated with PAH and pulmonary fibrosis                                    |
| Anti-U3RNP (fibrillarin) | 1%-6%                         | dcSSc > lcSSc Associated with PAH, myopathy, and severe disease                    |
| Anti-U1RNP              | 5%-35%                        | lcSSc > dcSSc Associated SSC overlap syndromes, where features of SLE, RA, MCTD, and myositis may be seen Concomitant anti-Ro/SSA, anti-La/SSB, and anti-Smith antibodies are common |

Table 2. Common autoantibodies associated with systemic sclerosis. Abbreviations: dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
studies involving referral populations. Conversely, left atrial diameter > 4.4 cm is often associated with left atrial hypertension, and this can be a useful measurement when considering the likelihood that a patient has PH from left heart disease.27

RIGHT HEART CATHETERIZATION

A diagnosis of PH requires right heart catheterization (RHC), which is used to measure pulmonary artery pressure directly. Additional important information from RHC includes PAWP to assess left heart pressure, right atrial pressure, and CO or cardiac index. From these data, the PVR is calculated from the following formula: \( \frac{(mPAP-PAWP)}{CO} \). Additional information from RHC that is useful includes measurement of blood oxyhemoglobin saturation level at different vascular or cardiac compartments including the mixed venous oxygen saturation level, which enables identification of a significant “step-up” or “step-down” in saturations consistent with the presence of an intracardiac shunt (defined as a change in the oxyhemoglobin saturation level beyond what is expected for normal variation between measurements, usually approximately \( \pm 4\% \)). When there is high suspicion for intracardiac or extracardiac shunt, direct oximetric sampling of the pulmonary veins can be considered to calculate the shunt fraction (\( Qp/Qs \)), which quantifies the directionality of blood flow through the shunt (reviewed in greater detail in reference 29).28

Error or artifact during hemodynamic measurement may misclassify PH and lead to inappropriate therapy (Table 3).29-32 Care must be taken to position the table-mounted transducer at the level of the patient’s phebostatic axis, conventionally defined by the intersection of the midaxillary line and a transverse plane passing through the fourth intercostal space. The transducer should be “zeroed” to atmospheric pressure at the start of the procedure, and ideally, prior to every pressure measurement, as drift in the transducer signal can occur over time. In patients with markedly elevated mPAP, obtaining a reliable PAWP tracing may be challenging due to incomplete catheter balloon occlusion of a dilated pulmonary artery branch. In these patients, “hybrid” pressure tracings—resembling a fusion of the pulmonary artery and PAWP waveforms—can raise the PAWP spuriously and imply a diagnosis of left-sided heart failure or valvular disease (Figure 1). The reliability of a given PAWP measurement can be tested through measurement of blood oximetry in the pulmonary artery wedge position, concordance with other PAWP values measured in a different anatomic region, or direct measurement of left ventricular end-diastolic pressure.

Despite direct assessment of cardio-pulmonary hemodynamics with RHC, controversy remains regarding the

Table 3. Common sources of error and artifact during right heart catheterization. Abbreviations: LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension.31,32

| Source of Error                       | Corrective Action                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------------|
| Improper transducer leveling         | Position table-mounted transducer in the midaxillary line at the level of the fourth intercostal space May need to be readjusted if the patient changes position |
| Transducer drift                     | Zero the transducer prior to each pressure measurement Replace transducer if there is difficulty maintaining zero |
| Excessive respirophasic pressure variation | Read pressures at end expiration (functional residual capacity) Consider coaching the patient’s breathing pattern (“skip your next breath”) or performing an end-expiratory hold in mechanically ventilated patients |
| Over-dampening                       | Check system for loose connections, air bubbles, kinks, thrombus, blood, or residual radiographic contrast agent Can be caused by “over-wedgeing” due to excessive balloon inflation pressure. *May increase risk of PA rupture* Minimize length of transducer tubing |
| Dicrotic notch, a, and/or v waves blunted or absent | *Eliminate air bubbles in the system Eliminate extra loops in the catheter Reposition the catheter Digital filter* |
| **Under-dampening**                  | **Overshoot or ring artifact** - high frequency spikes projecting above and below the true systolic and diastolic pressures, respectively **Fling or whip artifact** - rapid acceleration of the catheter tip caused by a hyperdynamic circulation or redundant loop in the catheter May falsely widen pulse pressure |
|                                      | Eliminate air bubbles in the system Eliminate extra loops in the catheter Reposition the catheter Digital filter |
| Hybrid waveform (also known as “under-wedged”) | Waveform resembles a composite of the PA and PAWP tracings due to incomplete wedging of the catheter balloon in a dilated PA branch. Often seen in the setting of marked PH Distinct a and/or v waves may still be present Spuriously elevates the PAWP relative to the LVEDP |
|                                      | Partially deflate balloon and advance into a more distal wedge position Reposition catheter to a different PA branch Confirm adequate PAWP via oximetry, fluoroscopy (with or without radiographic contrast injection), and measurement from multiple PA branches Direct measurement of LVEDP |
Figure 1: Hybrid PAWP waveform in a patient with pulmonary hypertension. A) The initial PAWP waveform (red) demonstrates accentuated \( v \) waves, and when compared to a simultaneous LV pressure tracing (yellow), a pressure gradient between the PAWP and LVEDP, which implies the possibility of mitral stenosis. However, incomplete balloon occlusion of the PA branch is proven by the oxygen saturation of 72% in blood withdrawn from the catheter tip. B) After catheter repositioning, the PAWP waveform demonstrates more characteristic morphology, the PAWP decreases and more closely approximates the LVEDP, and blood sampled from the catheter tip demonstrates an oxygen saturation of 95%. Abbreviations: LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure. Reprinted from Ragosta M. Normal Waveforms, Artifacts, and Pitfalls. In: Ragosta M. Textbook of Clinical Hemodynamics. 1st ed. Philadelphia, PA: Elsevier Saunders; 2008, with permission from Elsevier.

optimal strategy for reporting various measurements. For example, some clinical experts support end-expiratory measurement of PAWP as most accurate owing to wide respirophasic variation in intracardiac pressure that is observed some patients, particularly among those with COPD, although this practice is not uniform.\(^{29,30}\) Similarly, debate on the accuracy of CO when measured by thermodilution compared with the assumed Fick methods have persisted for many years. Recently, fresh data using mortality as an endpoint to determine the relative accuracy of each suggests that thermodilution is the preferred assessment strategy in clinical practice, although patient-specific characteristics including the presence of severe tricuspid regurgitation remains important to consider when interpreting data in an individual patient.\(^{31}\)

Information from RHC may be supplemented with vasoreactivity testing, pulmonary angiography, left heart catheterization, or provocative maneuvers depending on the clinical context. Vasoreactivity testing with inhaled nitric oxide should only be used in those with idiopathic or heritable PAH. It informs long-term prognosis and identifies the small population of patients who may gain substantial clinical benefit from calcium channel blocker therapy; as such, it is a key part of the diagnostic evaluation.\(^{34}\) Conversely, when there is a high suspicion for PH caused by left heart disease, a fluid challenge in the catheterization laboratory or invasive cardiopulmonary exercise testing (iCPET) may unmask left atrial hypertension that is not apparent on standard resting supine RHC. For example, PAWP >18 after an intravenous crystalloid bolus of 7 mL/kg revealed occult postcapillary PH in 8% of patients with apparent normal mPAP and 6% of patients with apparent precapillary PH during resting supine RHC.\(^{35}\) Nonetheless, standardized guidelines for performing and interpreting confrontational fluid challenge remain lacking. Similarly, controversy remains whether exercise or fluid challenge is a more effective provocative test for eliciting occult postcapillary PH.\(^{35}\) In patients referred for iCPET, the upper limit of normal for upright PAWP at peak exercise has been reported as 9±5 to 14.9±7.9 mm Hg depending on the cohort and may be age-dependent.\(^{36,37}\)

**PULMONARY FUNCTION TESTING AND ARTERIAL BLOOD GAS**

Lung disease is common in the general population and is particularly prevalent among patients referred for evaluation of dyspnea or exercise intolerance. Further, overlap between primary lung disease among patients with established PH risk factors, including left heart disease, is under-recognized thereby emphasizing the need for comprehensive clinical assessment among at-risk patients. Indeed, a standard diagnostic approach to PH will often include an objective assessment of lung function. The details of pulmonary function test (PFT) interpretation have been reviewed extensively previously.\(^{38}\) Patients with idiopathic PAH (IPAH) typically demonstrate normal spirometry and normal to modestly reduced lung volumes.\(^{39}\) Pulmonary hypertension arising in the setting of parenchymal lung diseases may be associated with more marked obstructive, restrictive, or combined ventilatory defects. It has been suggested that low diffusion capacity of carbon monoxide (DLCO) may be diagnostic of PH, but the wide range of diseases associated with alveolar-capillary interface remodeling diminish the diagnostic utility of this measurement. On the other hand, reduced DLCO is commonly observed in pulmonary vascular diseases and has prognostic value.\(^{40,41}\) Marked reduction in DLCO may be seen in IPAH, systemic sclerosis-associated PAH, PH in the setting of parenchymal lung diseases, or pulmonary veno-occlusive disease (PVOD). In PAH, the resting partial pressure of oxygen (PaO\(_2\)) may be normal or mildly decreased, although the alveolar-arterial oxygen gradient is usually increased. A chronic respiratory alkalosis is often observed due to resting alveolar hyperventilation; however, the physiologic mechanism by which hyperventilation occurs in PAH remains unknown.\(^{42}\)
VTELLATION/PERFUSION NUCLEAR SCAN AND COMPUTED TOMOGRAPHIC IMAGING

Chronic thromboembolic pulmonary hypertension is an important cause of PH because it is often curable by surgical endarterectomy. Evaluation at an experienced CTEPH program is suggested, which may extend clinical benefit to those patients with more distal vessel involvement or more severe hemodynamic compromise. For the ~35% of CTEPH patients that are inoperable (or refractory to surgical therapy), pharmacological intervention and/or balloon pulmonary angioplasty are effective treatments. Nonetheless, CTEPH is often overlooked: by most estimates, appropriate evaluation is completed in a minority of at-risk patients. In CTEPH, in situ thrombotic vascular remodeling of distal pulmonary arterioles results in the formation of webs, strictures, and bands causing mechanical obstruction to normal blood flow. Assessment by ventilation/perfusion (V/Q) scan remains the test of choice to diagnose CTEPH due to its exceptional sensitivity and specificity, which approach 100%, respectively, in some patient series. However, in “real-world” clinical practice, V/Q scan findings may be equivocal and are often insufficient to base clinical decision making in the setting of potential surgical intervention. Thus, advances in spatial resolution and the option for 3-dimensional reconstruction provided by modern computed tomographic (CT) and magnetic resonance imaging has replaced pulmonary angiography as the test of choice at many centers for both diagnosing and staging CTEPH. In the case of thoracic CT imaging, assessment of the lung parenchymal can also be useful in patients with competing causes of PH or PH-associated symptoms.

CARDIAC MAGNETIC RESONANCE IMAGING

Owing to the importance of RV function and the limited accuracy of quantifying RV geometry and ejection fraction by echocardiography, many experts integrate cardiac magnetic resonance (CMR) imaging into the evaluation of PH patients. This is particularly useful in patients for whom acoustic windows are insufficient and echocardiographically derived data on RV function is not known or may be abnormal. Indeed, a decrease in RV ejection fraction has prognostic implications in PAH, particularly <35%, and as such can be a useful treatment target. The precise role of RV late gadolinium enhancement, which can be indicative of fibrotic scar, in the clinical management of PH patients remains unresolved. Although CMR may also be useful diagnostically by unmasking important causes of PH such as structural or infiltrative heart disease misdiagnosed by echocardiography, its limited availability, higher cost, prolonged testing time, and issues related to claustrophobia during testing are often cited as barriers to the routine use in PH care.

EXERCISE TESTING

Standard (noninvasive) CPET can aid in risk stratification of newly diagnosed PH. Likewise, symptom-limited exercise that includes pneumotachometer, pulse oximeter, ECG, and metabolic cart analysis may suggest a PH diagnosis in patients with unexplained exertional dyspnea. Reduced oxygen uptake at peak exercise, early anaerobic threshold, ventilatory inefficiency (most commonly measured as an elevated minute ventilation relative to carbon dioxide [CO₂] production), increased arterial-to-end-tidal CO₂ gradient, reduced oxygen pulse, and exertional hypoxemia can be observed. In cases of particular diagnostic uncertainty, iCPET may be performed using radial and pulmonary artery catheterization in addition to standard CPET monitors to unmask an abnormal pulmonary vascular response to exercise or occult left atrial hypertension. Finally, submaximal exercise testing in the form of a 6-minute walk evaluation has been shown to correlate with PH clinical outcomes and hemodynamics, and is an accessible tool for risk stratification of incident PH in the office.

SPECIAL CONSIDERATIONS

Specific subsets of PH deserve mention, including PVOD, pulmonary capillary hemangiomatosis (PCH), PH in pregnancy, PH in the perioperative setting, and pediatric PH. While a detailed discussion of each condition is outside the scope of this article, it is important to emphasize that the care of these populations mandates multidisciplinary management at a specialized PH center. Although PVOD and PCH are uncommon, these disorders are likely underdiagnosed. Since lung transplantation is the only currently available disease-specific therapy, it is crucial to establish the diagnosis in a timely fashion. Likewise, prompt diagnosis is imperative in the setting of pregnancy, as PAH confers a 30% to 56% risk of peripartum mortality.

CONCLUSION

Diagnosing PH requires a multidimensional approach that considers comorbid rheumatologic, pulmonary, cardiac, infectious, and vascular diseases. Maintaining a wide differential diagnosis of symptoms that are often common, particularly dyspnea, is challenging. Overall, a detailed history and physical examination is likely to yield key clues on the presence of PH and, possibly, specific pulmonary vascular disease subtypes such as PAH. Careful interpretation of echocardiography data regardless of test indications must include analysis of the RV geometry and systolic function among other variables. Once confirmed by RHC, pursuing a clear cause of PH is accomplished through additional tests that are used largely to confirm or exclude potential etiologies. This is a critical and often complex aspect of the PH patient evaluation, as prognosis and treatment selection are determined solely by a correct diagnosis. Changes to the diagnostic criteria for PH may result from the forthcoming 2018 World Symposium on Pulmonary Hypertension. Overall, referral to PH expert centers is recommended for comanagement of patients, to optimize clinical decision making and potentially outcome.

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