Ask the Expert

Diagnosis of PAH From a Pulmonologist Perspective

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The axiom "diagnosis drives treatment" is especially important when evaluating patients with pulmonary hypertension (PH). Patients with PH, defined as a mean pulmonary arterial pressure (mPAP) greater than 25 mm Hg, are placed into 2 main categories based on hemodynamic measurements, pathophysiological mechanisms, clinical presentation, and therapeutic options. Patients with Group 1 disease, referred to as pulmonary arterial hypertension (PAH), have an mPAP >25 mm Hg with a normal pulmonary wedge pressure of 15 mm Hg or less and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Group 1 consists of 3 main subgroups: idiopathic PAH, familial PAH, and PAH associated with known risk factors or associated conditions (APAH).[1] The second category of patients with PH (Groups 2-5) includes patients with PH associated with left heart disease (Group 2), disorders of the respiratory system and/or hypoxemia (Group 3), chronic thromboembolic disease (Group 4), and obstruction of pulmonary vessels by processes including inflammation, mechanical obstruction, or extrinsic compression (Group 5).[1]

The diagnosis of PAH requires 3 sequential elements: 1) identifying patients with a high likelihood of PAH; 2) obtaining a transthoracic echocardiogram; and 3) performance of right heart catheterization in patients with an echocardiogram suggesting PAH. Clinical history, family history, and physical examination are helpful in identifying patients with an increased likelihood of PAH. Patients with specific medical conditions and genetic susceptibilities are predisposed to the development of PAH. Medical conditions associated with the development of PAH include systemic sclerosis (prevalence 8%-27%), HIV infection (prevalence 0.5%), portal hypertension (prevalence 4% in patients evaluated for liver transplant), prior appetite suppressant use, congenital heart disease with shunt, and sickle cell disease.[2] The primary genetic substrate for developing PAH includes patients with the bone morphogenetic protein receptor type II (BMPR2) mutation (prevalence 20%) and those with a family pedigree with 2 or more relatives with PAH.[2] The most frequent presenting symptom of PAH is exertional dyspnea, with fatigue and weakness also common. As the disease progresses chest pain, dizziness, syncope, palpitations, and lower extremity edema often develop.[3] Since the symptoms of PAH are nonspecific, they are often attributed to more common conditions and the diagnosis is often delayed. In a recent large registry of PAH patients, 21% of patients diagnosed with PAH reported symptoms for greater than 2 years before their disease was recognized. Younger patients (less than 36 years of age) and patients with coexistent common respiratory disorders, including obstructive lung disease, and sleep apnea were most likely to experience delayed PAH recognition.[4]

Physical examination findings are often subtle in patients with PAH, and the sensitivity and specificity of specific signs are not well documented. As PAH severity progresses, the signs become more clinically apparent and include the holosystolic murmur of tricuspid regurgitation, a prominent pulmonary component of the second heart sound, a midsystolic ejection murmur caused by turbulent pulmonary valve flow, a palpable right ventricular (RV) heave at the left parasternal area, an RV S4 gallop, and a prominent jugular "a" wave suggesting elevated RV filling pressures. Severe PAH results in RV failure manifested by an RV S3 gallop, jugular venous distention with an accentuated V wave, hepatojugular reflux, and peripheral edema.

Further diagnostic tests should be performed to provide evidence for known PAH risk factors, including liver function tests and connective tissue disease and HIV serologies. A chest x-ray and electrocardiogram (ECG) should also be obtained to reveal features supporting the diagnosis of PAH or to provide evidence for other disease processes associated with PH. Pulmonary function testing (PFT) is also an essential test in the evaluation of patients with suspected or confirmed PH. Spirometry, lung volume measurements, and carbon monoxide diffusing capacity should be obtained to diagnose obstructive or restrictive disease indicating Group 3 PH. The typical PFT pattern associated with PAH is a reduction in diffusing capacity and normal spirometry and lung volumes. However, 20%-50% of patients with PAH exhibit a restrictive defect in the absence of parenchymal lung disease.[5,6] Ventilation-perfusion (V/Q) scanning should be performed in all patients with PH to rule out chronic thromboembolic disease.[7] While computerized tomography (CT) angiography has largely supplanted V/Q scanning as the procedure of choice in the diagnosis of acute pulmonary embolism, V/Q scanning remains the preferred initial test to evaluate the possibility of chronic thromboembolic disease. It is unlikely that V/Q scanning will provide clinically important information in patients that have had a normal CT angiogram using current thin slice protocols.

In patients with a clinical suspicion for PAH, echocardiography is the screening test of choice. Current guidelines also recommend annual screening echocardiography in patients with systemic sclerosis, sickle cell disease, and carriers of the BMPR2 mutation in the absence of symp-

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toms.[2] An elevated estimated RV systolic pressure, defined as greater than 35-40 mm Hg, should lead to diagnostic heart catheterization in patients with suspected PAH. Echocardiography may also provide evidence for left sided heart disease, valvular heart disease, or congenital heart disease with intracardiac shunt. Echocardiography has significant limitations as a diagnostic procedure. It provides an estimate of RV systolic pressure that is assumed to correlate with pulmonary artery (PA) systolic pressure but cannot measure mPAP. Echocardiography also cannot reliably quantify pulmonary wedge pressure and thus distinguish between PAH and postcapillary PH. It is clear that echocardiography cannot replace cardiac catheterization as the definitive diagnostic tool for patients with suspected PAH.[7]

Right heart catheterization (RHC) is required in all patients with suspected PAH to confirm the diagnosis, assess severity, guide management, and exclude non-Group 1 PH diagnoses. The clinical utility of RHC depends on the accuracy and completeness for the data obtained. By convention, hemodynamic measurements are obtained at end exhalation. It is also good practice to review the hemodynamic tracings to confirm that the measurements are accurate. The essential measurements captured during RHC include PA pressure (systolic, diastolic, and mean), RV pressure, right atrium (RA) pressure, wedge pressure, cardiac output/index, oxygen saturations (SVC, IVC, RA, RV, PA), and response to vasodilator administration. If an accurate wedge pressure cannot be obtained, left ventricular end diastolic pressure should be measured.[2]

PAH is a devastating disease that is challenging for pulmonologists to diagnose. Timely diagnosis is imperative as it leads to initiation of therapy that improves patients' lives.

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