REVIEW

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Diagnostic strategies for suspected pulmonary arterial hypertension: A primer for the internist

ABSTRACT

Pulmonary arterial hypertension should be considered in patients who present with nonspecific symptoms such as dyspnea or dizziness after more common causes have been ruled out. Echocardiography can help in the diagnosis: special attention should be given to assess the tricuspid valve and right ventricular function. Before starting treatment, a patient should undergo right heart catheterization to accurately measure the pressures and assess right ventricular function, which help in appropriate selection of therapy.

KEY POINTS

Pulmonary hypertension can be associated with a variety of conditions, including collagen vascular diseases, congestive heart failure, parenchymal lung diseases, sleep apnea, and liver cirrhosis.

Doppler echocardiography is used for screening but is not reliable enough to be used for diagnosis.

Patients suspected of having pulmonary arterial hypertension should be evaluated with electrocardiography, imaging studies, pulmonary function tests, and serologic testing to assess the severity of disease and to identify associated conditions.

Measuring exercise tolerance and hemodynamics is essential for diagnosing early pulmonary arterial hypertension and in predicting survival and response to therapy.

Editor's note: This is the first of two articles by Drs. Minai and Budev on pulmonary arterial hypertension. They will review the treatment of this disease in an upcoming issue.

PULMONARY ARTERIAL HYPERTENSION is a disorder of which internists and primary care physicians should be aware, as it presents with common symptoms such as shortness of breath, chest pain, and fatigue, and as it can be due to several common diseases. Furthermore, if not promptly recognized and treated, it can have devastating consequences, including right heart failure and death.

Recent advances in the understanding of the pathophysiology and natural history of the condition have led to improved diagnostic strategies, but early and accurate diagnosis remains the foremost challenge.

This article reviews the current classification system of pulmonary arterial hypertension, examines causes and risk factors, and details diagnostic strategies.

WHAT ARE THE ESSENTIAL ELEMENTS OF ITS PATHOBIOLOGY?

Pulmonary arterial hypertension is defined as a resting mean pulmonary arterial pressure greater than 25 mm Hg with a mean pulmonary arterial occlusion pressure less than 15 mm Hg.[1]

*Dr. Minai has indicated that he has received honoraria for speaking and consulting for the Actelion Pharma, Encysure Pharma, Pfizer, and United Therapeutics corporations.

Although much remains to be learned about the genetic and environmental causes of pulmonary arterial hypertension, significant advances have occurred in the last 3 decades. Three major factors have been found to be associated with increased pulmonary vascular resistance: pulmonary vascular remodeling, thrombosis, and vasoconstriction.[2]

Vascular remodeling is probably the most important factor.[3] Its hallmark is the presence of smooth muscle cells in the small pulmonary arteries of the respiratory acini, which normally do not contain smooth muscle.[4] Vascular inflammation and endothelial cell proliferation contribute to vascular remodeling and the formation of plexiform lesions.

Platelet dysfunction and thrombosis are universal in pulmonary arterial hypertension and contribute to increased vascular resistance. Whether platelet dysfunction and thrombosis actually increase vascular pressure or result from it is uncertain.[5]

Vasoconstriction appears to result from both endothelial dysfunction and abnormal voltage-gated potassium channels in arterial smooth muscle. Endothelial dysfunction results in an overproduction of vasoconstrictors such as endothelin-1 and an underproduction of vasodilators such as nitric oxide, prostacyclin, and vasoactive intestinal peptide. This imbalance not only causes vasoconstriction but also promotes vascular remodeling. In addition, the voltage-gated potassium channels that normally participate in hypoxic pulmonary vasoconstriction seem to be decreased in number ("down-regulated") and function abnormally.[5]

Diagnosing pulmonary hypertension early remains challenging, since it is uncommon and its symptoms are nonspecific

WHAT IS ITS CLINICAL COURSE?

On the basis of our understanding of its pathophysiology and hemodynamic alterations, the course of pulmonary arterial hypertension can be divided conceptually into three phases (FIGURE 1):

The asymptomatic compensated phase. Abnormal cellular processes and resulting vascular remodeling begin to produce subtle hemodynamic alterations. The pulmonary vascular resistance gradually rises with a resultant increase in right ventricular afterload. The patient, however, has no symptoms because the increasing pulmonary vascular resistance and pulmonary arterial pressure are met with right ventricular hypertrophy and resultant preservation of cardiac output.

The duration of this phase is unclear, since these patients are rarely encountered; it may vary depending on the cause of the pulmonary hypertension.

The symptomatic decompensating phase comes next. Compensatory mechanisms such as right ventricular dilation, increased sympathetic outflow producing increased heart rate and contractility, and activation of the renin-angiotensin-aldosterone system play an increasingly prominent role in the face of progressive increases in pulmonary vascular resistance and pulmonary arterial pressure. Despite increased sympathetic drive and intravascular volume, cardiac output begins to fall as right ventricular function declines.

Patients develop shortness of breath as the initial symptom and are often labeled as having asthma or being overweight or deconditioned. As the right ventricle fails, right atrial pressure increases significantly, and patients develop shortness of breath, fatigue, dizziness, abdominal bloating, lower extremity edema, and gradually increasing functional limitation. At this stage, the nonspecific nature of these symptoms typically prompts a workup for common cardiac and pulmonary causes, and a diagnosis of pulmonary hypertension is eventually made.

The duration of this phase may vary from months to years depending on etiology and the adequacy of treatment.

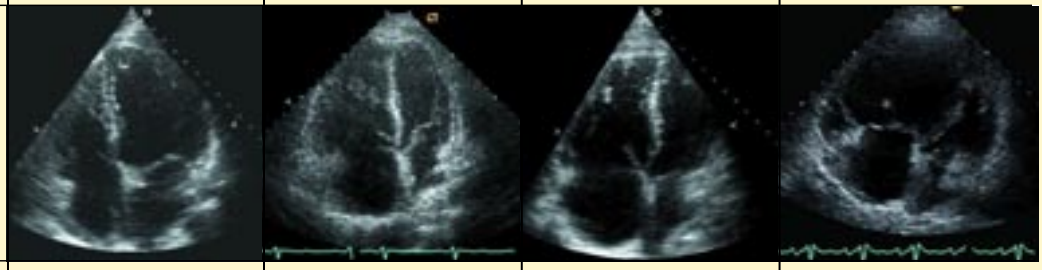
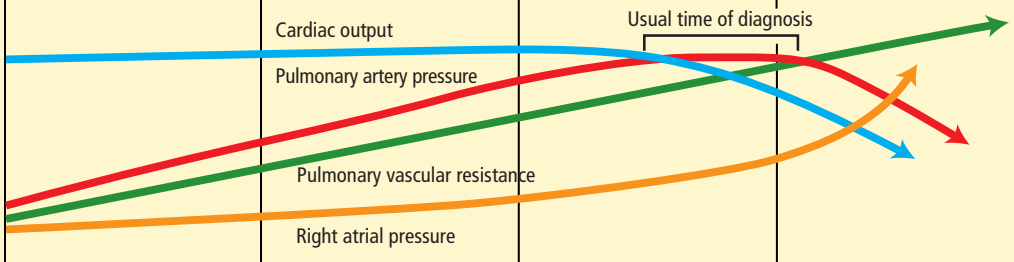
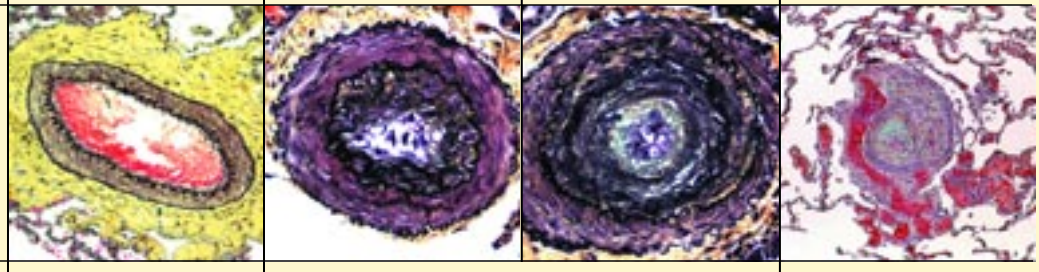
The advanced decompensated phase, the third phase, is marked by a progressive increase in pulmonary vascular resistance and right atrial pressure with an accompanying decline in cardiac output. When the right ventricle cannot generate adequate systolic force, the pulmonary arterial pressure actually falls.

Patients in this phase manifest worsening symptoms of right ventricular failure with progressive, severe functional limitation eventually resulting in death.

HOW DO WE CLASSIFY AND STAGE PULMONARY HYPERTENSION?

Before 1998, pulmonary hypertension was classified as either primary or secondary,

Pulmonary arterial hypertension: Clinical course and progression

PHASE	ASYMPTOMATIC COMPENSATED	SYMPTOMATIC DECOMPENSATING		ADVANCED DECOMPENSATED
		SUBTLE	OVERT	
Symptoms and signs	None	Shortness of breath, fatigue	Shortness of breath, fatigue, pedal edema, dizziness, abdominal swelling, right ventricular dysfunction	Right ventricular failure, syncope, death
Functional class	I	II	III	IV
Echocardiographic appearance				
Hemodynamic trends (not drawn to scale)				
Pathologic appearance				
Duration	Unclear (? years)	Months to years		Months
Suspected diagnosis	None	Asthma, overweight, deconditioning, psychosomatic condition, depression	Congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, pulmonary embolism, deconditioning, occult interstitial lung disease	Pulmonary hypertension

ECHOCARDIOGRAMS COURTESY OF DRS. LEONARDO RODRIGUEZ AND WILLIAM STEWART; PHOTOMICROGRAPHS COURTESY OF DR. CAROL FARVER.

FIGURE 1

TABLE 1

Revised clinical classification of pulmonary hypertension

Pulmonary arterial hypertension
Idiopathic
Familial
Associated with:
- Collagen vascular disease
- Congenital systemic-to-pulmonary shunts
- Portal hypertension
- Human immunodeficiency virus infection
- Drugs and toxins
- Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)

Associated with significant venous or capillary involvement
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

Persistent pulmonary hypertension of the newborn

Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease

Pulmonary hypertension associated with lung diseases or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

Pulmonary hypertension due to chronic thrombotic or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

FROM SIMONNEAU G, GALIE N, RUBIN LJ, ET AL. CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION. J AM COLL CARDIOL 2004; 43:5S–12S.

Pulmonary arterial hypertension involves remodeling, thrombosis, and vasoconstriction

TABLE 2

World Health Organization classification of functional status of patients with pulmonary hypertension

Class I	No limitation of usual activity
Class II	Slight limitation of usual physical activity
Class III	Marked limitation of usual physical activity
Class IV	Inability to perform any physical activity without symptoms and possible signs of right heart failure

ADAPTED FROM RUBIN LJ; AMERICAN COLLEGE OF CHEST PHYSICIANS. DIAGNOSIS AND MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION: ACCP EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES. CHEST 2004; 126:7S–10S.

depending on risk factors and associated conditions. Primary pulmonary hypertension was essentially a diagnosis of exclusion.

In 1998, the Second World Symposium on Pulmonary Hypertension created a new classification that divided pulmonary hypertension into five categories based on the pathophysiology and natural history of the disease.

The 2003 Third World Symposium modified the system further. The term "primary pulmonary arterial hypertension" was abandoned and replaced with "idiopathic pulmonary arterial hypertension" (TABLE 1).[6] This symposium also stressed that staging of pulmonary hypertension should be based on functional capacity using the World Health Organization classification system, a modified form of the New York Heart Association functional class system, rather than on hemodynamic variables alone (TABLE 2).[1]

IS SCREENING FEASIBLE? WHICH STRATEGIES WORK BEST?

Detecting and treating pulmonary arterial hypertension early in its course is thought to improve functional capacity and the survival rate, but diagnosing the disease can be a challenge because its incidence is low and its signs and symptoms are nonspecific. Most cases are not clinically obvious until the disease is advanced.[7]

Because the prevalence in the general population is low, screening for early disease should be reserved for people at moderate to high risk of developing it, eg:

- First-degree relatives of patients with pulmonary arterial hypertension
- Patients with congenital heart disease with systemic-to-pulmonary shunts
- Patients with collagen vascular diseases.

The condition is also more likely in patients with predisposing conditions such as human immunodeficiency virus (HIV) infection or portal hypertension and in patients who have taken the weight-loss drugs aminorex, fenfluramine, or dexfenfluramine.

TABLE 3 lists risk factors associated with pulmonary arterial hypertension.[8,9]

TABLE 3

Risk factors for pulmonary arterial hypertension

Drugs and toxins
Definite
- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil

Very likely
- Amphetamines
- L-tryptophan

Possible
- Meta-amphetamines
- Cocaine
- Chemotherapeutic agents

Unlikely
- Antidepressants
- Oral contraceptives
- Estrogen therapy
- Cigarette smoking

Demographic and medical conditions
Definite
- Female sex

Possible
- Pregnancy
- Systemic hypertension

Unlikely
- Obesity

Diseases
Definite
- Human immunodeficiency virus infection

Very likely
- Portal hypertension or liver disease
- Connective tissue diseases
- Congenital systemic-pulmonary cardiac shunts

Possible
- Thyroid disorders
- Hematologic conditions
  - Asplenia secondary to surgical splenectomy
  - Sickle cell disease
  - Beta-thalassemia
  - Chronic myeloproliferative disorders
- Rare genetic or metabolic diseases
  - Type 1a glycogen storage disease (von Gierke disease)
  - Gaucher disease
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)

FROM GALIE N, TORBICKI A, BARST R, ET AL; TASK FORCE. GUIDELINES ON DIAGNOSIS AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION. THE TASK FORCE ON DIAGNOSIS AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION OF THE EUROPEAN SOCIETY OF CARDIOLOGY. EUR HEART J 2004; 25:2243–2278.

TABLE 4

Schema for evaluating a patient with suspected pulmonary arterial hypertension

	EVALUATION	ACTION IF DETECTED
PULMONARY HYPERTENSION SUSPECTED	History and physical examination Chest radiography	Right and possibly left heart catheterization Rule out in turn possible causes of pulmonary hypertension listed below
POSSIBLE CAUSES		
Left heart disease (including systolic, diastolic dysfunction or valvular disease)	Right and possibly left heart catheterization	Appropriate treatment of left heart disease
Congenital heart disease	Echocardiography with contrast (transthoracic or transesophageal) Right and possibly left heart catheterization	Medical vs surgical management
Connective tissue disease (systemic sclerosis, systemic lupus erythematosus, others)	Blood tests	Appropriate treatment
HIV, liver disease	Blood tests	Appropriate treatment
Chronic thromboembolic pulmonary hypertension	Ventilation-perfusion scan	Pulmonary angiography Thromboendarterectomy if appropriate Medical therapy (clotting evaluation, anticoagulation; consider vasoactive agents)
Lung disease, hypoxemia	Pulmonary function tests Oxygen saturation with exertion and sleep Chest radiography and/or computed tomography Sleep study if needed	Oxygen Optimize medical therapy for lung disease
Familial disease	Family history of pulmonary hypertension or unexplained sudden death	Genetic counseling and testing for patients with suspected familial pulmonary arterial hypertension
ASSESSMENT OF FUNCTIONAL LIMITATION AND PROGNOSIS		
Functional limitations	World Health Organization class 6-minute walking test	
Hemodynamics	Right heart catheterization, with or without vasodilator testing	

ADAPTED FROM MCGOON M, GUTTERMAN D, STEEN V, ET AL; AMERICAN COLLEGE OF CHEST PHYSICIANS. SCREENING, EARLY DETECTION, AND DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION: ACCP EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES. CHEST 2004; 126:14S–34S.

Screening methods are limited

Although Doppler echocardiography is preferred for screening, evidence supporting this use is limited.[10] In experienced centers, exercise echocardiography may have a role to play in screening high-risk populations.[11]

Cardiopulmonary exercise testing has been suggested for screening because the anaerobic threshold and oxygen consumption at peak exercise are abnormal in patients with pulmonary arterial hypertension, but its lack of reliability and availability have limited its use.[8,12]

The role of prenatal testing for the purpose of pregnancy termination in positive cases is controversial. Only 10% to 20% of

fetuses identified develop clinically significant disease later.[12]

Patients suspected of having pulmonary arterial hypertension should be tested to confirm the diagnosis and evaluated for disorders that may have caused the condition. Disease severity and complications should also be assessed (**TABLE 4**).[10,13]

WHAT CLUES CAN BE OBTAINED FROM THE HISTORY AND PHYSICAL?

Patients suspected of having pulmonary hypertension should undergo a detailed history and physical examination. Patients usually present with symptoms of impaired oxygen transport and reduced cardiac output, including dyspnea, fatigue, exercise intolerance, difficulty with activities of daily living, chest pain, and syncope. Exertional dyspnea, the most common presenting symptom, occurs in almost all patients as the disease progresses.[14]

A number of conditions may be associated with pulmonary hypertension and should be evaluated, including concomitant left-sided cardiac disease, valvular heart disease, parenchymal lung diseases, sleep apnea, collagen vascular diseases, and hepatic disorders.[15]

Patients should be asked about their use of illicit drugs, appetite suppressants, herbal medications, and supplements.

Signs of pulmonary arterial hypertension are often subtle and can be easily overlooked early on. The diagnosis is more likely in the presence of[14–16]:

- An accentuated pulmonary component of the second heart sound caused by delayed closure of the pulmonary valve
- An early systolic ejection click caused by interruption of the pulmonic valve opening
- A midsystolic ejection murmur caused by turbulent blood flow across the pulmonary valve
- A palpable left parasternal lift
- A right S_4 gallop
- A prominent jugular *a* wave, suggesting high ventricular filling pressure.

An augmented inspiratory holosystolic murmur of tricuspid regurgitation and hepatojugular reflux are signs of more advanced disease. A right ventricular S_3 gallop, marked jugular venous distention, a pulsatile liver, ascites, and peripheral edema indicate right ventricular failure. Cool extremities and findings of hypotension indicate poor cardiac output and peripheral vasoconstriction that may herald cardiac collapse. Cyanotic digits may indicate a right-to-left shunt. Digital clubbing, although rarely found in pulmonary arterial hypertension, raises the possibility of congenital heart disease or pulmonary veno-occlusive disease.[17]

Pulmonary arterial hypertension

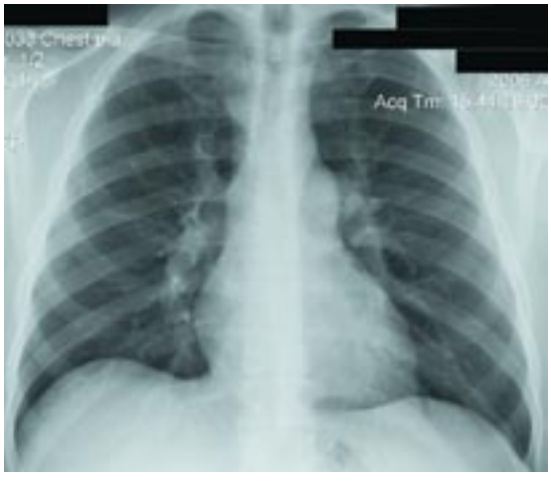


FIGURE 2. The chest radiograph shows dilated central pulmonary arteries with peripheral pruning.

Signs of pulmonary arterial hypertension are often subtle and easily overlooked early on

WHAT IS THE ROLE OF ELECTROCARDIOGRAPHY AND IMAGING STUDIES?

Electrocardiography is not sensitive enough to be an effective screening tool for pulmonary arterial hypertension, but it can provide prognostic information and establish a baseline.[10] Echocardiographic findings of right atrial enlargement, right ventricular enlargement, and right axis deviation should prompt further evaluation.

Chest radiography should be done, although it is neither sensitive nor specific enough to establish a diagnosis. It can help identify chronic obstructive pulmonary disease, interstitial lung disease, and kyphosis. Right ventricular or pulmonary artery enlargement may be seen, or the typical pattern of central vessel enlargement with peripheral pruning or attenuated peripheral markings may be present (**FIGURE 2**).

Computed tomography (CT) of the chest with high-resolution cuts should be performed to evaluate mediastinal disorders involving the central pulmonary vasculature and early interstitial lung disease.

Ventilation-perfusion scanning is preferred for screening for chronic thromboembolic disease. Patients with a normal scan need no further evaluation for thromboembolic disease, but those with one or more segmental-sized mismatched perfusion defects should undergo pulmonary angiography for accurate diagnosis and to assess if surgery is indicated.[18]

Magnetic resonance imaging (MRI) can measure mean pulmonary arterial pressure and right ventricular chamber size and thickness and may provide better information than that obtained from echocardiography.[19,20] However, the American College of Chest Physicians[10] does not advocate the routine use of MRI to evaluate patients with newly diagnosed pulmonary arterial hypertension because its value over the more traditional noninvasive methods has not been established.

IS DOPPLER ECHOCARDIOGRAPHY THE BEST NONINVASIVE TEST?

Patients with suspected pulmonary arterial hypertension should undergo echocardiography

Doppler transthoracic echocardiography is essential for evaluating pulmonary hypertension but cannot be used to make a diagnosis of pulmonary hypertension. Right ventricular systolic pressure (RVSP) can be estimated using a modified Bernoulli equation (RSVP = $4v^2$ + right atrial pressure), where v is the velocity of the tricuspid regurgitant jet in meters per second. Pulmonary hypertension is suspected in patients with an RVSP of more than 40 mm Hg. However, RVSP values lower than 50 mm Hg should be interpreted with caution when pulmonary hypertension is suspected.

The low prevalence of pulmonary hypertension confers a low pretest probability of a positive result, reducing the sensitivity and specificity of echocardiography as a screening tool. Using RVSP, Doppler echocardiography is 79% to 100% sensitive and 60% to 98% specific for identifying pulmonary hypertension.[10]

Studies[21–23] have reported that RSVP estimated by echocardiography is closely correlated to RSVP measured by right heart catheterization (r value 0.57–0.95). Although the correlation is generally strong in patient groups, mean differences between the studies in individual patients are as high as 38 mm Hg.[10] A high discordance is most evident at extremes of pulmonary pressures and in patients with underlying lung disease.[24]

Echocardiography can help assess left heart disease contributing to pulmonary hypertension by evaluating left ventricular function and detecting diastolic dysfunction as well as valvular heart disease. It can also estimate the degree of right chamber enlargement and dilation and detect the presence of right ventricular hypertrophy, pulmonary artery dilation, pericardial effusion, and right ventricular function. Another use is to detect an intracardiac shunt in patients with hypoxia, using the bubble technique.

Global right ventricular dysfunction and indicators of chronically elevated right-sided filling pressures such as a pericardial effusion and leftward bowing of the interventricular septum (the "D sign") are reported to be associated with poor prognosis.[25,26]

Changes in RVSP cannot reliably be used to follow response to vasoactive therapy.

The role of exercise echocardiography is not well defined but is an area of research.

Although pulmonary arterial hypertension can be suspected on the basis of echocardiography, the diagnosis should be confirmed by right heart catheterization before starting therapy.

SHOULD PULMONARY FUNCTION AND FUNCTIONAL CAPACITY BE ASSESSED?

At their initial evaluation, patients with suspected pulmonary arterial hypertension should undergo pulmonary function testing, including spirometry, determination of lung volumes, and evaluation of the diffusing capacity for carbon monoxide (D_{LCO}). Pulmonary function testing helps to identify any significant parenchymal lung, airway, or chest wall disorder that may be relevant to the etiology of pulmonary hypertension.[15] Although the D_{LCO} does not correlate with the severity of pulmonary arterial hypertension, a value that is out of proportion to the decline in forced vital

capacity is one of the earliest signs of pulmonary arterial hypertension in patients with systemic sclerosis,[27] and a value less than 55% in a patient with systemic sclerosis without pulmonary fibrosis may indicate an increased risk of developing pulmonary arterial hypertension within 5 years.

Prolonged hypoxemia is integral to the development of pulmonary hypertension in patients with advanced parenchymal lung disease. Hypoxemia in pulmonary arterial hypertension is typically mild or moderate and is believed to result from low mixed venous oxygen saturation and ventilation-perfusion mismatching. Severe hypoxemia is uncommon and is believed to be due to intrapulmonary or intracardiac shunting.

Measuring exercise tolerance and desaturation are essential for diagnosing pulmonary arterial hypertension early and predicting survival and response to therapy.[28,29] Serial measurement of 6-minute walking distance is a simple and useful tool for following patients over time. Paciocco et al[30] found that a drop in the arterial oxygen saturation of more than 10% during 6-minute walking was associated with a 2.9 times increased risk of death over a median follow-up of 26 months.

Minai et al[31] found that nocturnal oxygen desaturation occurs in up to 70% of patients with idiopathic pulmonary arterial hypertension without significant sleep apnea. Nocturnal hypoxemia was more common in older patients with more advanced pulmonary hypertension and right ventricular dysfunction. About 60% of patients without exertional hypoxia had nocturnal desaturation, indicating that a lack of exertional hypoxia cannot rule out nocturnal hypoxia.

All patients with pulmonary hypertension should undergo testing to determine whether hypoxia occurs with exercise or sleep. No further nighttime testing is needed if overnight oximetry on room air shows no desaturation, but an abnormal result requires a full polysomnographic study to diagnose and determine the extent of sleep apnea. If hypoxia is detected, patients should be given supplemental oxygen during exertion and while asleep to keep oxygen saturation levels above 90% to avoid the pulmonary vasoconstrictive effects of hypoxemia.

WHAT IS THE ROLE OF SEROLOGIC TESTING AND BIOMARKERS?

Basic serologic testing for evaluating a patient with pulmonary arterial hypertension includes a complete blood cell count, arterial blood gas measurement, complete metabolic panel, thyroid function tests, aminotransferase levels, antiphospholipid antibody titers, testing for collagen vascular diseases (with antinuclear antibodies), and HIV testing. A baseline level of brain natriuretic peptide should also be obtained and may have prognostic value as a marker of response to therapy or disease progression.[16]

Other blood tests, including uric acid and troponin levels, are currently confined to research and are not routinely measured for diagnosis or follow-up.

DO ALL PATIENTS REQUIRE RIGHT HEART CATHETERIZATION?

Although elevated brain natriuretic peptide levels and echocardiographic changes may suggest pulmonary hypertension, the current recommendations strongly advise performing right heart catheterization to formally make the diagnosis.[10] All patients who are being considered for therapy should undergo the procedure.

The 6-minute walking test is a simple and useful tool for following patients over time

Right heart catheterization may provide additional information (by direct measurement or calculation) of right atrial pressure, mixed venous oxygen saturation, pulmonary artery occlusion pressure, cardiac output and index, and pulmonary vascular resistance. It can also detect a congenital cardiac defect and estimate left-sided pressures to assess pulmonary venous hypertension secondary to conditions such as mitral valve disease and diastolic dysfunction. Pressure measurements may also help assess prognosis and long-term effects of new treatments.[7]

If right heart catheterization confirms pulmonary arterial hypertension, a vasodilator should be given to determine the degree of pulmonary arterial vasoreactivity. No consensus exists as to which agent should be used; intravenous epoprostenol (Flolan), intravenous adenosine, or inhaled nitric oxide is

usually chosen, owing to the potent, short-acting vasodilatory effects. A patient is deemed "vasoresponsive" if the vasodilator causes the mean pulmonary arterial pressure to decrease by at least 10 mm Hg to a level of 40 mm Hg or lower, with an unchanged or increased cardiac output.[32]

Only 10% to 15% of patients are likely to have a positive vasodilator response. A positive response is less common in patients with pulmonary arterial hypertension associated with collagen vascular diseases than in patients with idiopathic disease.

Vasoresponsiveness may identify patients who are likely to have a good long-term response to treatment with calcium channel blockers alone.

MANAGEMENT REQUIRES A TEAM

Optimal care requires a partnership between the patient, pulmonary specialist, cardiologist, and rheumatologist at a center specializing in pulmonary hypertension, as well as with local physicians caring for the patient.[33]

Multicenter trials have led to the approval of parenteral, inhaled, and oral vasoactive agents that act as pulmonary vasodilators and also possess antithrombotic, antifibrotic, and antimitogenic properties.[34–38] Recent evidence suggests that monotherapy[39–41] or combination therapy[42–44] may provide sustained benefit.

We will discuss the treatment of pulmonary arterial hypertension in greater detail in a future article in this journal.

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