The Ochsner Journal 9:234–240, 2009

Pulmonary Hypertension for Primary Care Providers

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ABSTRACT

Pulmonary hypertension is a constellation of diseases that shares signs and symptoms of dyspnea, fatigue, chest pain, palpitations, and syncope. Research advances made over the past decade have significantly changed the natural history of this disease. Therapies initially designed to specifically target the molecular causes of increased pulmonary vascular resistance are now used in all types of patients with pulmonary hypertension. The challenge of the primary care physician is first, identifying pulmonary hypertension, and second, determining the modifiable substrates that contribute to the development and symptoms of this disease.

A 27-year-old woman was referred by her company's doctor for syncope. She was told to follow up with a primary care physician after she passed out at work. She reported that there was no seizure activity, and she was unconscious for less than a minute. She remembers waking up and feeling okay. She described a similar episode when she was in graduate school; after wearing an electrical heart-recording device for a day, she was told there was nothing wrong with her. The only other past medical history she reported is asthma diagnosed in college. She has had no surgeries, and there is no family history of disease. Her only prescribed medication is albuterol. She reported having an old canister that was given to her by Student Health because she was getting short of breath during intramural soccer; it never helped her breathing problem. A review of systems is pertinent for exercise intolerance and dyspnea on exertion, with negative findings for wheezing, orthostatic dizziness, or any neurologic deficits. Her examination was remarkable for a body mass index of 27, oxygen saturation 93%, an accentuated S_2, and a holosystolic murmur at the base that augments with inspiration. No blood work was performed at this visit. What laboratory examination would you like to perform? Are there any other tests you might order?

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Disclosures: Dr. Patel has been a consultant and speaker for Gilead, Actelion, and United Therapeutic Corporation.

Key Words: Chest pain, dyspnea, pulmonary arterial hypertension, pulmonary hypertension, syncope

Respiratory complaints are a common presenting problem for emergency department and primary care physicians, making it an easy topic for discussion on didactic rounds and in textbooks. However, the determination of the specific pathophysiology for respiratory complaints is not always easy to discern. Pulmonary hypertension (PH) is increasingly believed to a play a larger role in a variety of patients' complaints (ie, dyspnea, fatigue, chest pain, and syncope). The case at the beginning of this article illustrates some of the common presenting signs and symptoms of pulmonary hypertension but also demonstrates some of the pitfalls in diagnosis.

Pulmonary hypertension is best described as a syndrome of dyspnea-related symptoms in the presence of a mean pulmonary arterial pressure of >25 mmHg, regardless of mechanism. Pulmonary hypertensive disorders are classified into groups on the basis of underlying mechanisms, clinical context, and histopathology (Table 1).[1] This classification system is the most recent consensus of worldwide opinion regarding a disease that was not organized until 1973.[2]

Normal pulmonary vasculature is a low-pressure system with less than one tenth the resistance observed systemically. Pulmonary arterial hypertension (PAH) more specifically pertains to the hemodynamic profile in which high pulmonary pressure is produced by elevation of precapillary pulmonary resistance. Thus for a diagnosis of PAH, the mean pulmonary artery pressure must be >25 mmHg in the setting of normal or reduced cardiac output and a normal pulmonary capillary wedge pressure, normal left atrial pressure, and pulmonary vascular resistance >3 Wood units.[3] This distinction is important as all forms of PAH reduce survival,[4] and correct identification of the clinical context in which PAH occurs allows for appropriately tailored therapy to optimize therapeutic results.

Table 1. Revised World Health Organization Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension (PAH)
   - 1.1. Idiopathic (IPAH)
   - 1.2. Familial (FPAH)
   - 1.3. Associated with (APAH):
     - 1.3.1. Connective tissue disorder
     - 1.3.2. Congenital systemic-to-pulmonary shunts
     - 1.3.3. Portal hypertension
     - 1.3.4. HIV infection
     - 1.3.5. Drugs and toxins
     - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   - 1.4. Associated with significant venous or capillary involvement
     - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - 2.1. Left-sided atrial or ventricular heart disease
   - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Sleep disordered breathing
   - 3.4. Alveolar hypoventilation disorders
   - 3.5. Chronic exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous

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

* Reprinted with permission from Simonneau G, Galiè N, Rubin L, et al.[1]

EPIDEMIOLOGY

Multiple pathogenic pathways have been implicated in the development of PAH, both at the molecular and genetic levels affecting the smooth muscle, endothelial cells, and/or adventitia. The evolution of pulmonary vascular disease proceeds via a concept referred to as the *multiple-hit hypothesis*.[5] This model describes the interaction of a predisposing state and one or more inciting stimuli, in the activation of various mechanisms to create imbalance in the vasoconstrictor/vasodilator milieu (ie, an additional genetic condition, a coexisting disease, or an environmental exposure). This imbalance ultimately leads to a triad of vascular constriction, cellular proliferation, and a prothrombotic state.

Although PAH was previously considered a rare disease, the most recent evidence from a French registry suggests that the prevalence of PAH is about 15 per million.[6] Idiopathic pulmonary arterial hypertension was the most prevalent type of PAH in the French registry, with reports of its incidence of 2 million to 5 million per year.[7] Idiopathic PAH is most prevalent in women, with a male to female ratio of 1.7:1 and a mean age at diagnosis of 37 years. Familial pulmonary arterial hypertension is documented in 6% to 10% of patients with PAH.[8] The most common mutation, found in 50% to 90% of patients, is in the bone morphogenic protein receptor-2 (BMPR2), which is inherited as an autosomal dominant disease with incomplete penetrance and genetic anticipation.[9] Amphetamines, notably the appetite suppressants aminorex, fenfluramine, and dexfenfluramine, have been shown to increase the odds of developing PAH by a factor of 6.3.[10] These causes—

Table 2. Pulmonary Arterial Hypertension (PAH): Determinants of Prognosis*

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (>400 m)	Shorter (<300 m)
CPET	Peak V_{O_2} >10.4 mL/kg per minute	Peak VO_2 <10.4 mL/kg per minute
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/ dysfunction, right atrial enlargement
Hemodynamics	RAP <10 mmHg, CI >2.5 L/min per square meter	RAP >20 mmHg, CI <2 L/min per square meter
BNP§	Minimally elevated	Significantly elevated

* Most data available pertain to idiopathic PAH; few data are available for other forms of PAH. One should not rely on any single factor to make risk predictions. RV=right ventricular; WHO=World Health Organization; 6MW=6-minute walk; CPET=cardiopulmonary exercise testing; peak V_{O_2}=average peak oxygen uptake during exercise; RAP=right atrial pressure; CI=cardiac index; BNP=brain natriuretic peptide. Reprinted with permission from McLaughlin VV, Archer SL, Badesch DB, et al.[17]

† WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.

‡ 6MW distance is also influenced by age, sex, and height.

§ Because there are currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and sex may influence BNP, absolute numbers are not given for this variable.

idiopathic, familial, and anorexigen-induced PAH—formerly encompassed the diagnosis of primary PH.

Pulmonary arterial hypertension occurs with sufficient frequency in the course of other disease that it has specific features to warrant classification. Connective tissue disease (CTD), especially the scleroderma spectrum, is an important subgroup. Based on a Doppler echographic definition of estimated right ventricular systolic pressure >40 mmHg, PH is present in 23% of patients with scleroderma or mixed CTD.[11] An estimated 64% to 80% of individuals with limited cutaneous systemic sclerosis have histopathologic changes consistent with PAH. However, fewer than 10% of patients with limited cutaneous systemic sclerosis develop clinically apparent disease.[12] The overall incidence of congenital heart disease is approximately 8 per 1,000 live births and approximately 30% of children who do not undergo surgical repair of systemic-to-pulmonary shunts will develop pulmonary vascular disease.[13] PAH associated with portal hypertension is found in 2% to 6% of patients referred for liver transplantation.[14] Studies of patients with human immunodeficiency virus (HIV) infection show an incidence of PAH of 0.5%.[15] More recent

Table 3. Physical Signs That Suggest Possible Underlying Cause or Associations of Pulmonary Hypertension*

Sign	Association
Central cyanosis	Abnormal V/Q, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic pulmonary hypertension
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

* V/Q=ventilation perfusion. Reprinted with permission from McLaughlin VV, Archer SL, Badesch DB, et al.[17]

Table 4. Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension (PH)*

Sign	Implication
Physical Signs That Reflect Severity of PH	
Accentuated pulmonary component of S_2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular *a* wave	Poor right ventricular compliance
Physical Signs That Suggest Moderate to Severe PH	
Moderate to severe PH	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular *v* waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S_3 (in 23%)	Right ventricular dysfunction
Distension of jugular veins	Right ventricular dysfunction or tricuspid regurgitation or both
Hepatomegaly	Right ventricular dysfunction or tricuspid regurgitation or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction

* Reprinted with permission from McLaughlin VV, Archer SL, Badesch DB, et al.[17]

studies also show an increasing prevalence, approaching 10% to 30%, of identified PH in patients with sickle cell disease.[16]

Aside from PAH, other types of PH have less characterized effects but are believed to exist in the similar vasoconstrictive milieu. For instance, some degree of PH is present in almost 66% of patients with stage IV chronic obstructive pulmonary disease. Severe PH may similarly develop in patients with sleep-disorder breathing, obesity hypoventilation syndromes, and chronic hypoxemia; studies have shown worse survival in these patients with PH disproportional to their pulmonary disease.[17] Chronic thromboembolic PH is observed in up to 3% of patients with acute pulmonary embolism.[18] When chronic thromboembolic PH is left untreated, the probability of survival at 5 years is 30%.[19]

NATURAL HISTORY

The natural history of idiopathic PAH was described by the National Institutes of Health registry, which enrolled 194 patients at 32 clinical centers from 1981 to 1985.[7] This registry best characterizes the untreated responses of patients with idiopathic PAH prior to medical therapy. The data from this registry show 1-, 3-, and 5-year survival rates of untreated patients at 68%, 48%, and 34%, respectively.[20] Later research showed that associated conditions can influence outcomes. Patients with CTD- and HIV-associated PAH have worse prognosis, while those with congenital heart disease-associated PAH have a better prognosis.[4] Overall, the prognosis of PAH is poor, with a mortality of approximately 15% within 1 year for patients receiving modern therapy.[21]

As recently as the Third World Conference on PH in Venice in 2003, predictors of poor prognosis were revalidated and include advanced functional class, poor exercise capacity as measured by 6-minute walk or cardiopulmonary exercise test, high right atrial pressure, significant right ventricular dysfunction, evidence of right ventricular failure, low cardiac index, elevated brain natriuretic peptide, and underlying

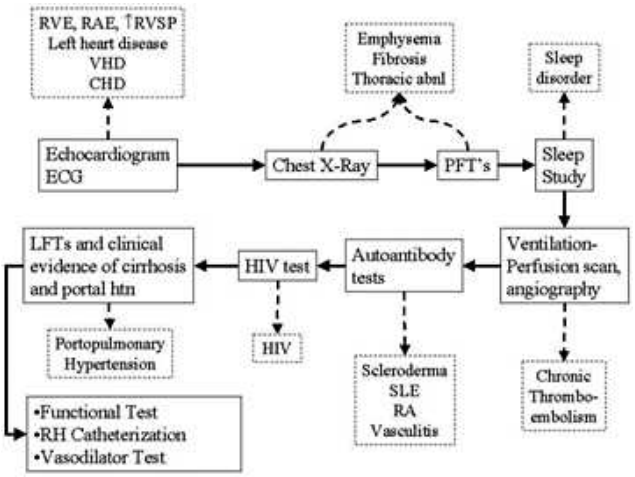

Figure 1. Diagnostic algorithm for the evaluation of pulmonary arterial hypertension. RVE=right ventricular enlargement; RAE=right arterial enlargement; RVSP=right ventricular systolic pressure; VHD=valvular heart disease; CHD=congenital heart disease; LFT's=liver function tests; htn=hypertension; RH=right heart; abnl=abnormality; PFT's=pulmonary function tests; SLE=systemic lupus erythematous; RA=rheumatoid arthritis. Reprinted with permission from McLaughlin, McGoon MD.[2]

diagnosis of scleroderma spectrum of disease (Table 2).[17] The ability to place an individual patient in higher versus lower risk helps to define prognosis[22] and helps guide therapy.

CLINICAL ASSESSMENT

The general practitioner's primary role in the process of evaluating suspected PH is more commonly oriented toward confirming its presence and identifying associated disease substrate. A PH specialist is oriented toward defining the specific hemodynamic contributions, identifying the underlying cause, determining prognosis, and identifying the most appropriate therapy.

Because of the low prevalence of PH in the general population, global screening is inadvisable. In patients in whom a physician suspects PH, the recommended method of 1-time screening is Doppler echocardiography.[17] The frequency of PAH in certain populations, however, warrants periodic assessment, and a clinician's role is to identify through dutiful family and medical history those patients at risk or with the substrate to warrant assessment. These include patients with family members with known genetic mutations, patients with CTD, or patients with HIV. The optimal frequency of assessment is unclear, but annual assessment is reasonable in these high-risk patients.[2]

In addition to medical and family history, a thorough review of systems and a physical examination should be performed. The aim is to identify and better characterize the common symptoms of dyspnea on exertion, fatigue, chest pain, syncope, palpitations, or lower extremity edema. These symptoms in the context of heightened clinical suspicion and appropriate physical signs (Table 3)[17] can be suggestive of the underlying disease association. Physical examination findings may be useful in guiding the need for further assessment, both as an indicator of disease severity and as a means of deciding aggressiveness of treatment (Table 4).[17]

The most important components of the initial assessment of PH are to recognize the common overlapping diagnoses that create confusion in this relatively healthy patient population. The majority of testing is designed to help rule out or confirm contributing diagnosis (Figure 1).[2] As mentioned previously, initial assessment should involve Doppler echocardiography, not only to confirm the presence of PH but also to assess left heart disease, congenital heart disease, chamber size, function, and valvular heart disease. As dyspnea is a common concern in most patients with PH, obtaining a chest x-ray and pulmonary function testing and polysomnography should be performed to assess for emphysema, fibrosis, thoracic abnormalities, and sleep disorders. If any suspicion of chronic thromboembolism remains, a ventilation perfusion scan or contrast angiography should be performed. The prognostic influences of disease-associated PAH warrant screen laboratory examinations for HIV, CTD, and liver disease. Functional testing, right heart catheterization, and vasodilator testing are usually undertaken by a specialist once the diagnosis of PH has been made.

TREATMENT OPTIONS

Medical therapy for PAH has made significant progress over the past 20 years (Figure 2).[23] A thorough presentation of the finer points and nuances of appropriate medical therapy for PH is beyond the scope of this article, although recently released algorithms outline expert opinion.[24] Instead, an overview of medications used in treatment of PAH will be discussed.

Oral therapy is often the first-line therapy for PAH, partly because of the ease of administration and patient preference. The 2 classes of oral agents currently available for PAH are endothelial antagonists and phosphodiesterase-5 inhibitors. Depending on the side effect profiles of these drugs and patient-specific risk factors (including New York Heart Association stage of disease), most PH specialists will begin administration of the endothelial antagonists bosentan (Tracleer) and ambrisentan (Letairis) and/or the phosphodiesterase-5 inhibitors sildenafil (Revatio) and tadalafil (Adcirca) as first-line oral therapy.

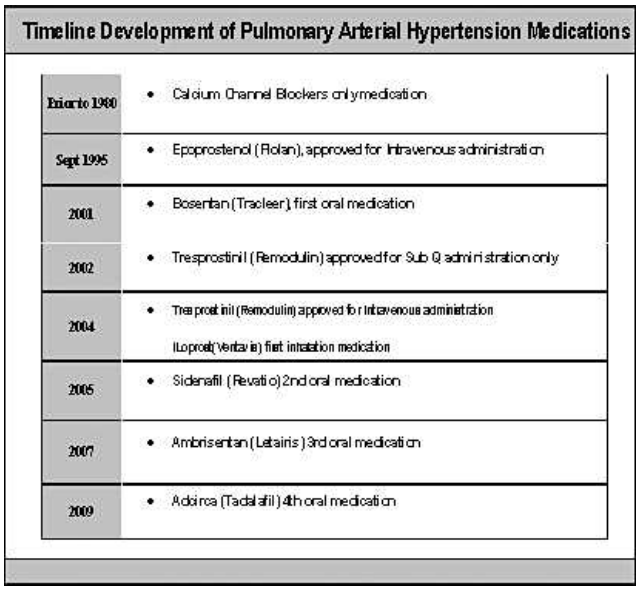

Figure 2. Timeline of pulmonary arterial hypertension medications.

If the patient's disease continues to progress or if the patient presents with advanced right heart failure, prostacyclin-based therapy may be used. Prostacyclin-based therapy has 3 Food and Drug Administration-approved routes of therapy: subcutaneous, intravenous, and inhaled. Once again, clinicians balance the side effect profile and the patient-specific risk factors to help determine the best prostacyclin-based therapy for the patient.

Two areas of contention in PAH therapy are placebo arms for research studies and combination therapy. Although the data are limited on survival benefits from the aforementioned oral drugs, many institutional review boards and industry leaders think that it is inappropriate to continue to have placebo arms in clinical trials. The decrease in placebo control trials in PAH research naturally leads to combination therapy as the future standard for PH drug therapy.

Despite the increase in the number of medical options available for PAH therapy, cost continues to limit the number of patients who can be treated. The medications listed here can cost anywhere from $10,000 per year for oral therapies to hundreds of thousands of dollars per year for the intravenous and inhaled therapies.

CONCLUSION

PAH is a constellation of diseases, with significant impact on financial, societal, and individual levels. PH is increasingly being identified as a contributor to patient morbidity. Although it might be unnecessarily alarming to describe every patient with hemodynamic PH as being at risk, it is clear that clinically important PH encompasses far more than the traditionally discussed patient with PAH (World Health Organization classification 1).

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