PH: Classification and Diagnosis

In this Issue...

Pulmonary hypertension (PH) is a progressive disease characterized by severe remodeling of the distal pulmonary vasculature; without treatment, the condition leads irremediably to death through right ventricular failure.

In this issue of ePulmonology Review, Paul M. Hassoun, MD, Professor of Medicine and Director of the Pulmonary Hypertension Program at The Johns Hopkins University School of Medicine in Baltimore, reviews and analyzes the current literature redefining and reclassifying PH and the most recent evidence (both pharmacological and pharmacoeconomic) supporting the use of up-front combination therapy vs monotherapy in patients with pulmonary arterial hypertension (PAH).

LEARNING OBJECTIVES

- Identify the current classification of pulmonary hypertension (PH) based on groups of diseases sharing similar pathology.
- Outline a basic algorithm for diagnostic workup of various etiologies of PH.
- Discuss the principles of therapy currently available, and specific indications for the five groups of the PH classification.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

Paul M. Hassoun, MD
Professor of Medicine
Director, Pulmonary Hypertension Program
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Guest Faculty Disclosure

Dr. Hassoun has indicated that he has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

Unlabeled/Unapproved uses

Dr. Hassoun has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

IN THIS ISSUE

COMMENTARY

Classification of Pulmonary Hypertension

Pulmonary Arterial Pressure During Rest and

Program Directors

Gregory B. Diette, MD
Professor of Medicine, Epidemiology and
Pulmonary hypertension (PH) is a progressive disease of the pulmonary vasculature which, if left untreated, leads irremediably to right ventricular failure and premature death. Even when treated, PH is a source of significant morbidity and mortality. The underlying pathophysiology is complex and remains generally poorly understood. However, remodeling of the three layers (intima, media, and adventitia) of the small pulmonary arterioles is recognized as the principal pathologic feature of the syndrome and involves proliferation of endothelial cells, smooth muscle cells, and fibroblasts, as well as influx of various inflammatory cells such as B and T cells, increased expression of growth factors, and release of inflammatory cytokines locally and into the bloodstream.

The first classification of PH by experts in the field was prompted by a European epidemic of PH related to the use of an appetite suppressant, aminorex. Other epidemics of PH followed, such as the use of toxic rapeseed oil in Spain and appetite suppressants of the fenfluramine type in the US and Europe, spiking further interest in this syndrome.

So far, six world conferences have been held by groups of international experts on pulmonary hypertension, the most recent in Nice, France, in April 2018. However, the latest published classification, from the preceding meeting of experts also held in Nice, was in 2013. Five groups of PH have been identified, based on shared etiology, clinical characteristics, and pathophysiology.

The diagnosis of PH can be suspected on a clinical history, which typically leads to obtaining a screening echocardiogram. This may reveal an elevated estimated right ventricular systolic pressure and dilation of right-sided cardiac chambers. However, the diagnosis of PH is essentially obtained by right heart catheterization.

- **Group 1** (PAH) includes idiopathic (IPAH) and heritable PAH (with a familial history or presence of mutations in certain identified genes such as BMPR2, the most frequent gene implicated in heritable PAH, and also other genes such as ALK-1, endoglin, SMAD9, caveolin 1), PH associated with connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, and schistosomiasis. Group 1 also includes rare diseases that probably form a spectrum, including pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis.
- **Group 2** PH is characterized by an elevated pulmonary arterial wedge pressure $\geq 15$ mmHg and includes entities related to left heart disease (left ventricular systolic or diastolic dysfunction and valvular diseases).
- **Group 3** PH is related to chronic lung disease/hypoxia.
- **Group 4** is chronic thromboembolic PH (CTEPH).
- **Group 5** includes miscellaneous diseases with unclear multifactorial mechanisms (eg, sarcoidosis; hematologic and metabolic disorders).

Minor changes have been made to the most recent classification by disease group (to be published soon). However, PH is now defined as mean pulmonary arterial pressure (mPAP) obtained by right heart catheterization $\geq 20$ mmHg (instead of the previous 25 mmHg cutoff for the diagnosis) and pulmonary vascular resistance $\geq 3$ Wood units. This was decided based on values of mPAP in normal individuals, obtained from a review of 47 studies including over 1,000 individuals from various ages, which very rarely exceeded 20 mmHg at rest.² While a change in this definition should not result in an increased prevalence of patients with idiopathic PAH (who are normally diagnosed with delay, when they are typically with functional class II or III symptoms), this new definition will likely mean that more
patients at risk for the disease (for instance patients with CTD) with mPAP previously thought to be abnormal (between 20 mm Hg and 25 mmHg) will now have diagnoses of PAH and will benefit from PAH therapy. This change in definition is welcome for this group, considering that when followed over years, a mild elevation of mPAP is a predictor of mortality, and a significant number of these patients will indeed develop PAH over time.\(^3\)

Briefly, FDA-approved drugs essentially target three distinct pathways (the endothelin, nitric oxide, and prostacyclin pathways) and include a total of 12 drugs in oral, injectable, or inhaled forms. However, all efforts have been geared at group 1 PH (PAH), although group 2 (associated with left heart disease, such as left ventricular dysfunction or heart failure with preserved ejection fraction, HFpEF) is by far the most common form of PH and carries an overall one-year mortality of 41%.\(^4\) WHO group 3 (associated with lung disease) is the second most common form of PH and carries a one-year mortality of 46%\(^4\). Neither group 2 or 3 has any FDA-approved therapy. The treatment for group 4 PH (CTEPH) is primarily surgical (pulmonary artery endarterectomy, PEA, to be performed in specialized centers) in addition to oral therapy with riociguat\(^5\), a soluble guanylate cyclase stimulator, approved for inoperable and recurrent/persistent PH after PEA. This medication has also been approved for the treatment of PAH (group 1). Balloon pulmonary angioplasty is also rapidly gaining traction, in specialized centers, for patients with inoperable disease or as an adjunct therapy to surgery in selected patients.

A major shift of paradigm in the past few years in terms of medical therapy for PAH has been the recognition that combination therapy is far superior to monotherapy. Several large landmark trials are worth noting. The AMBITION trial\(^6\) tested the value of up-front combination therapy with ambrisentan and tadalafil compared to monotherapy for each drug. All patients in this trial were treatment naïve at the onset. The end-point in this trial was time to clinical failure, defined by the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. The results demonstrated unequivocally that patients receiving combination therapy had significantly fewer disease-related events than did patients taking monotherapy with either tadalafil or ambrisentan, irrespective of the PAH subgroup, including patients with CTD-associated PAH.

Another large trial, SERAPHIN\(^7\), demonstrated that the endothelin receptor antagonist macitentan compared to placebo resulted in fewer hospitalizations and delayed PAH worsening. In many cases, patients were already on background therapy (PDE-5 inhibitor or oral or inhaled prostanoid) in either the placebo or treatment arm. Similarly, the GRIPHON\(^8\) trial demonstrated that selexipag also reduced hospitalization and delayed disease progression in patients with PAH, while the PATENT-1\(^9\) and CHEST-1\(^10\) trials demonstrated that riociguat, a soluble guanylate cyclase stimulator, improved functional capacity (six-minute walk distance) in patients with PAH and inoperable or persistent CTEPH, respectively.

Individual PAH therapies are very costly, and combination therapy is even costlier. However, a recent report summarizing pharmacoeconomic studies demonstrated that modeling for increased pharmacy costs are partially offset by decreased health care utilization, in particular cost of hospitalization, including a cost benefit with combination therapy at two years.\(^11\)

References:

5. Mahmud E, Madani MM, Kim NH, Poch D, Ang L, Behnamfar O, Patel MP, Auger WR. Chronic Thromboembolic Pulmonary Hypertension: Evolving Therapeutic


Classification of Pulmonary Hypertension


This article summarizes the latest classification of pulmonary hypertension (PH) from the 5th World Symposium on PH that was held in Nice, France, in 2013. This classification was not significantly different from previous classifications of PH, with five general groups. The few modifications included moving PH associated with chronic hemolytic anemia from group 1 to group 5 (unclear/multifactorial mechanism) since mechanisms of PH related to these syndromes are multifactorial. Persistent pulmonary hypertension of the newborn (PPHN) was designated separately within group 1 (PAH) because of dissimilarities between this entity and adult PAH. Congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies were added to group 2, while no significant changes were made to groups 3 and 4.

It is expected that this classification of PH will remain fairly unchanged when the new classification from the 6th World Symposium on PH (also held in Nice in 2018) is published later this year. For now, this manuscript represents the most updated classification.
Pulmonary Arterial Pressure During Rest and Exercise


This article reviewed all accessible hemodynamic data obtained on 1,187 people included in 47 studies performed in 13 countries to assess the normal values of mean pulmonary arterial pressure (Ppa) at rest and with exercise. Data were stratified for age, sex, geographical position, and exercise level. The authors concluded that, while Ppa is independent of age and rarely exceeds 20 mmHg, exercise-related Ppa is age-dependent and often exceeds 30 mmHg, particularly in elderly people.

This article helped redefine normal Ppa at rest and with exercise. A new definition of PH (greater or equal to 20 mmHg with pulmonary vascular resistance > 3 Wood units) is expected to appear in the upcoming proceedings of the 2018 World Symposium on PH in Nice.

Increasing Incidence and Prevalence of PH


This 2018 publication reports on the incidence, prevalence, comorbidities, mortality, and prescribing patterns for groups 1 to 4 PH from 1993 to 2012 in the Ontario province of Canada (a cohort of 50,529 patients with PH). In the adult population, both incidence and prevalence of PH increased over the observation period. Group 2 PH was the most common form of PH (34.2%) alone or combined with group 3 (29.3%). A diagnosis of PH increased the one-year mortality about seven-fold, with mortality at five years being as high as 62.4%. Mortality was highest in groups 2 and 3 and lowest in group 1. In contrast, in children group 1 was the most common form (65.2%), and five-year mortality was 21.4%. PAH-specific therapies were increasingly prescribed over time and often for group 2 disease.

This article confirms the long-held view that group 2 PH (due to left heart disease) is the most common form of PH, at least in this area of the world (North America). It also shows that diagnosis of PH is on the rise, most likely related to increased awareness of the disease, and mortality from this syndrome remains high. Finally, PAH specific drugs (FDA-approved for group 1 PAH) are increasingly used for group 2 disease.

The authors of this 2018 publication assessed the impact of mild elevation in mean pulmonary arterial pressure (mPAP) in retrospective and prospective cohorts of patients with unexplained dyspnea and/or at risk of pulmonary hypertension. A CART (classification and regression tree) analysis on mPAP discriminated three different groups (mPAP less than 17 mmHg; mPAP between 17 and 26 mmHg; and mPAP greater than 26 mmHg) with progressively decreasing survival. The threshold of 17 mmHg and 26 mmHg and values between 20 mmHg and 25 mmHg represented independent predictors of survival. ([NCT 01607502](https://clinicaltrials.gov/ct2/results?term=NCT01607502))

This study reveals that elevated pulmonary pressure previously considered to be mild (e.g., between 17 mmHg and 26 mmHg) portends decreased survival compared to a low pressure (less than 17 mmHg). While PH was previously defined as mean pulmonary arterial pressure \( \geq 25 \) mmHg, it is likely that the new definition (emanating from the 6th World Conference of PH, 2018) will change to include any pressure \( \geq 20 \) mmHg. While this change in definition may not affect idiopathic PAH (IPAH), since those patients are often diagnosed late in their disease (when pressures are significantly above 25 mmHg), it will affect populations at risk (for instance patients with connective tissue disease) in which early detection and elevation of mean pulmonary arterial pressure greater than 20 mmHg will lead to earlier onset of therapy with FDA-approved drugs.


The authors prospectively evaluated the incidence of pulmonary hypertension (PH) and factors that could predict the later development of PH in a population of patients with systemic sclerosis, using univariate and multivariate analyses. Ninety-six patients with a mean pulmonary arterial pressure (mPAP) < 25 mmHg were followed for a median of three years. The likelihood of these patients later developing PH was significantly higher than in patients with normal mPAP. Pulmonary vascular resistance, tricuspid regurgitation velocity, DLCO, and the size of the inferior cava were all independent predictors of the development of PH at follow-up evaluation. In a select cohort of patients with low DLCO (< 60%), there was an increase in pulmonary pressures over time, and about 25% of these patients developed PH. The authors concluded that regular screening and performing right heart catheterization may be important in patients at risk for developing PH.

This is an important study, emphasizing the fact that elevations in pulmonary arterial pressure — < 25 mmHg, previously considered to be mild and perhaps insignificant — may be a harbinger of later development of PH. Thus, frequent screening and right heart catheterization during follow-up may be important to avoid missing a life-threatening diagnosis in this population at risk (scleroderma) for PH.
Early Intervention: Clinical and Economic Outcomes


Current evidence supports early intervention, often with initial combination therapy, to avoid the high morbidity and mortality rates of PAH. However, the expense of PAH-specific medications and the potential for serious adverse effects when used in combination has pointed out the need to better understand early intervention from an outcomes as well as an economic perspective.

A database search (PubMed, Scopus, Ovid, and MEDLINE; 2005 to 2017) for studies comparing clinical outcomes, drug cost, and hospitalization burden associated with PAH therapy found that:

- early therapy and combination therapy in particular for patients in WHO class 2 is beneficial. Concomitant hospitalizations also consistently decreased.
- increased pharmacy costs of combination therapy were partially offset by decreased health care utilization, particularly inpatient care.
- modeling found a cost benefit with combination therapy at two years.

These recent data suggest that early therapy and up-front combination therapy, although costly, may decrease costs in the long term and be beneficial to PH patients.

Initial Use of Ambrisentan plus Tadalafil in PAH


This event-driven, double-blind study sought to determine the effect of initial combination therapy with ambrisentan and tadalafil on long-term outcomes in patients with PAH. Five hundred participants with WHO class II or III symptoms, naïve to treatment, were randomized to:

- 10 mg of ambrisentan plus 40 mg of tadalafil (combination therapy group), or
- 10 mg of ambrisentan plus placebo (ambrisentan monotherapy group), or
- 40 mg of tadalafil plus placebo (tadalafil monotherapy group).

The primary end point in a time-to-event analysis was the first event of clinical failure, defined as a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. A primary end-point event occurred in:

- 18% — the combination therapy group
- 34% — the ambrisentan monotherapy group
- 28% — the tadalafil monotherapy group

At week 24, vs the pooled-monotherapy group, the combination-therapy group had:

- Greater reductions from baseline in N-terminal probrain natriuretic peptide levels (*P* < .001)
- A higher percentage of patients with a satisfactory clinical response (*P* = .03)
- A greater improvement from baseline in the six-minute walk distance (*P* < .001)

Adverse events occurring more frequently in the combination therapy group included
peripheral edema, headache, nasal congestion, and anemia.

The investigators concluded that in participants with PAH naïve to treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical failure than either of the agents as monotherapy.

Based on this trial, up-front combination therapy with an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor has become the therapeutic norm for patients with PAH. However, it is unclear at this time whether these findings can apply to specific drugs in either of the two classes of agents. In addition, the effect of up-front combination therapy on survival is also unclear, as there were no differences in mortality; death was rare in each of the three therapeutic groups.

KEY TAKEAWAYS

- Pulmonary hypertension (PH) is a severe syndrome which, left untreated, leads irremediably to death through right ventricular failure.
- There are five PH groups, according to the World Classification of PH, based on shared etiology, clinical characteristics, and pathophysiology.
- Currently FDA-approved drugs for group 1 disease (pulmonary arterial hypertension, PAH) target three distinct signaling pathways (eg, the endothelin, nitric oxide and prostacyclin pathways).

IMPORTANT CME/CE INFORMATION

ACCREDITATION STATEMENTS

Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT

Physicians
eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
eNewsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a
maximum of 1 contact hour, or a total of 3 contact hours for the 3 newsletters in this program.

**POLICY ON SPEAKER AND PROVIDER DISCLOSURE**

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies that will identify and resolve conflicts of interest prior to this educational activity. Detailed disclosure will be made prior to presentation of the education.

All rights reserved - The Johns Hopkins University School of Medicine. Copyright 2018.

This activity was developed in collaboration with DKBmed.