



## Approach to a patient with pulmonary hypertension

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### Abstract

Pulmonary hypertension is a common clinical condition that can complicate various cardiac and respiratory abnormalities. Interest in pulmonary hypertension has grown remarkably among the scientific community in the last decade. It is now clear based on the scientific advances have paved the way in understanding the effects of abnormal pulmonary hemodynamics development and its antecedent consequences on the right heart in reducing the quality of life and survival of the patient.

*J Geriatr Cardiol* 2019; 16: 478–481. doi:10.11909/j.issn.1671-5411.2019.06.007

**Keywords:** Pulmonary arterial hypertension

## 1 Introduction

Pulmonary hypertension (PH) is a common clinical disorder associated with varied heterogeneous group of diseases, classified into five groups as per the World Symposium on Pulmonary Hypertension (WSPH).<sup>[1]</sup> It is defined by pulmonary artery mean pressure of  $\geq 20$  mmHg at rest as assessed by right heart catheterization (RHC).<sup>[2]</sup> A significant proportion of PH occurs in patients with left-sided heart disease and lung disease. In the recent years, an effort to identify and treat PH has gained significant attention as its development is linked to prognosis in various clinical situations. Among the five groups, group one pulmonary arterial hypertension (PAH) characterized by significant advances with prolific development of impactful pharmacotherapeutic strategies that have been shown to significantly reduce the risk of clinical worsening but not mortality.<sup>[3]</sup> From diagnostic strategies standpoint, the use of provocative maneuvers like fluid challenge and exercise during RHC to elicit dynamic responses of the pulmonary artery wedge pressure (PAWP) to delineate the presence of left heart disease (LHD).<sup>[4,5]</sup> This has received attention in the recent years due to growing number of older people often with cardiovascular risk factors being referred to the PH specialist centers for PAH management and such therapy has been shown

to potentially cause harm in PH due to left heart disease (PH-LHD).<sup>[6]</sup> The following review was undertaken to provide new insights in the pathophysiology and the emerging clinical perspective's in the field of PH.

## 2 Pathophysiology

### 2.1 Clinical classification

PH encompasses a group of clinical entities that have categorized into five different groups based on the patient sub-groups with similar pathological findings, hemodynamic profiles and therapeutic management profiles. Such classification has enabled the scientific community to identify the gaps in knowledge and limitations in support of therapeutic innovation.<sup>[1]</sup>

### 2.2 PAH

PAH, rare form of PH, characterized by pulmonary vascular remodeling mainly affecting the small pulmonary arteries ultimately leading to rise in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), eventually culminating in progressive right heart failure and functional decline.<sup>[7]</sup> Since the initial WSPH proceedings, various scientific advances, have paved the way in identifying key cellular and molecular mechanisms that have been implicated in the pathobiology and are now being considered as emerging therapeutic targets. In addition, genetic factors and immune dysfunction have also been identified to play a role in the pathology. It is important to recognize that the available treatments do not specifically target pulmonary vascular remodeling and the inflammatory pathways impli-

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**Received:** March 14, 2019

**Revised:** May 30, 2019

**Accepted:** June 24, 2019

**Published online:** June 28, 2019

cated in the pathogenesis of the disease. From a pathology standpoint, plexiform vasculopathy is characteristic, but the pathophysiological significance of these specific lesions is yet to be elucidated at this time.<sup>[8]</sup>

### 2.3 PH-LHD

It is the most common forms of PH worldwide. Isolated post-capillary (Ipc-PH) and combined pre and post capillary PH (CPcPH) are two distinct hemodynamic phenotypes that occur in response to a passive increase in left-sided filling pressures. The two different phenotypes can be distinguished based on the elevated diastolic pressure gradient of  $\geq 7$  mmHg and PVR  $\geq 3$  wu obtained by right heart catheterization.<sup>[9]</sup> From pathology standpoint, elevated left heart filling pressures from the underlying cardiac disorder affects the structure and function of the pulmonary circulation, leading to pulmonary arterial and venular remodeling. In addition, the right ventricle is affected from the increase in afterload leading to right ventricle-pulmonary artery unit uncoupling leading to adverse outcomes. From management standpoint, the treatment essentially involves treatment of the underlying cardiac disorder. At this time, the guidelines maintain a strong recommendation against use of PAH-specific approved drugs. It is important to note that some of the existing clinical trial data signal harm towards using the PAH specific drugs in certain subset of patients with PH-LHD. *i.e.*, Fluid retention with use of macitentan in CPcPH and Sildenafil use post valvular heart disease intervention are associated with an increased risk of clinical deterioration and death.<sup>[9]</sup>

### 2.4 PH due to chronic lung disease (CLD)

PH-CLD frequently occurs in patients with severe lung disease. It is associated with reduced quality of life and confers increased mortality risk. The CLD comprises obstructive, restrictive and mixed forms. At this time, data do not exist to support the use of PAH-approved drugs for treatment in these patients.<sup>[10]</sup>

### 2.5 Chronic thromboembolic PH

It occurs as a complication of pulmonary embolism. Pooled incidence of 3.4% has been established from published prospective studies. Exact pathogenesis is still unclear at this time. Establishing early and accurate diagnosis by ventilation/perfusion scintigraphy (V/Q scan) is essential as pulmonary endarterectomy when performed can offer cure with reported three-year survival rates of 90% as noted in international registries. In patients deemed not a candidate for surgery due to inaccessible vascular obstruction, PAH specific medical therapy and balloon pulmonary an-

gioplasty have evolved as important component of treatment algorithm in the recent years.<sup>[11]</sup>

### 2.6 PH with unclear or multifactorial mechanisms

Multiple pathophysiological factors have been involved in the development of PH. Given the heterogeneity in the clinical presentations, currently no definitive diagnostic or management strategies exist at this time other than treatment of each specific subset.<sup>[12]</sup>

### 2.7 Diagnostic evaluation of PH

The diagnostic process for PH starts following a high index of suspicion, especially in patients with no apparent risk factors as symptoms are non-specific. Exertional dyspnea, fatigue, exercise intolerance, chest pain, weakness and syncope may characterize PH. Besides history and physical exam, chest X-ray, electrocardiography, blood tests and immunology, pulmonary function studies, transthoracic echocardiography, V/Q scan are essential tests that should be considered initially in the evaluation. Additional diagnostic tests include chest computed tomography and cardiopulmonary exercise testing aid in the comprehensive evaluation of a patient suspected with PH. It is important to note that the definitive diagnoses of the PH can only be established by invasive hemodynamic assessment and it forms an essential step in the diagnosis.<sup>[2]</sup>

### 2.8 Hemodynamic definition and classification

PH has been arbitrarily defined as pulmonary artery mean pressure of  $\geq 25$  mmHg at rest measured by RHC since the 1<sup>st</sup> WSPH meeting organized by World Health Organization in Geneva. This cut-off has enabled the scientific community to differentiate primary or pre-capillary PH from secondary or post capillary PH on the basis of PAWP or left ventricular end-diastolic pressure in situations where PAWP cannot be obtained thus precluding overdiagnosis and treatment.

### 2.9 Precapillary PH

Based on the report from Kovacs, *et al.*<sup>[13]</sup> in 2009, the normal mean pulmonary arterial pressure in healthy subjects is noted to be approximately  $14 \pm 3.3$  mmHg. Taken this into consideration, the upper limit of normal would identify a threshold of 20 mmHg for identifying abnormal PAP. Based on the accumulating data, the task force from the 6<sup>th</sup> WSPH have proposed that primary PH or pre-capillary PH is defined as an abnormal elevation in the mean PAP  $\geq 20$  mmHg and need for PVR  $\geq 3$  wu to define all forms of pre-capillary PH.<sup>[14]</sup> Once the diagnosis is established, it is essential to perform acute vasoreactivity testing for identifi-

cation of patients suitable for high dose calcium channel blockers treatment. It is important to note that such testing is only indicated for patients with idiopathic PAH, heritable PAH or drug induced PAH. Vasoreactivity defined as reduction of mean PAP  $\geq 10$  mmHg to reach an absolute value of mean PAP  $\leq 40$  mmHg with an increased or unchanged cardiac output. The testing can be performed using Inhaled NO 10-20 PPM has been established as standard of care by professional societies, but intravenous epoprostenol or adenosine or inhaled iloprost can be used as alternatives. Once vasoreactivity is established, patients should be treated with high dose calcium channel blockers and repeat hemodynamic assessment should be performed in 3-6 months and again at one year. If vasoreactivity is not established, then patient should be treated with approved PAH therapies as outlined in the treatment section. It is important to note that vasoreactivity testing is not indicated in PH-LHD, unless if it being performed in the context of heart transplantation.

For post-capillary PH, PAWP value of  $> 15$  mmHg measured at end-diastole and end-expiration is considered essential for diagnosis.<sup>[9]</sup> It is important to note that presence of significant large V-waves should be noted strongly in favor of PH due to LHD regardless of the wedge pressure. For patients with PAWP of 13-15 mmHg but with risk factors for left sided heart disease, a three-step approach to accurately characterize the clinical phenotype of PH due to LHD has been recently proposed by the task force. In addition, provocative testing with fluid challenge to uncover PH due to heart failure with preserved ejection fraction has been recently incorporated in the diagnostic algorithm. A PAWP  $> 18$  mmHg immediately after administration of 500 mL of normal saline over five min is considered abnormal.<sup>[4]</sup>

### 2.10 Risk stratification of PAH

Risk assessment has emerged as important part of patient care in estimating the prognosis of patients with PAH. Tools for risk assessment included the initial National Institute of Health Idiopathic PAH registry to the currently used registry to evaluate early and long-term PAH disease management 2.0 risk equation to predict all-cause hospitalization and mortality.<sup>[3]</sup>

The Multi-parametric risk stratification incorporating clinical, right ventricular function, exercise and hemodynamic parameters are used to define the patient risk and thus to determine treatment. Patients are classified into low, intermediate or high-risk status according to the expected one-year mortality with a treatment goal to achieve low risk status by available treatments. The methodical risk assessment and treatment strategy have been validated in large international registries to clearly show the event-free survival at baseline and at follow up.

## 3 Treatment of PH

Once the diagnosis of the PAH has been made, therapy includes general measures and supportive therapy. General measures include information on physical activity, avoidance of pregnancy as it is associated with a substantial mortality rate in PAH, and use of birth control but there is less consensus relating to the most appropriate methods of birth control, travel and genetic counseling. Supportive therapy includes use of oxygen, diuretics and digoxin.<sup>[1]</sup> With regards to oral anticoagulation, data is conflicting and also been proven to be harmful in associated PAH. Currently decision on use of anticoagulation should be individualized based on the risk-benefit analysis.<sup>[15]</sup>

Significant advances have been made in the supportive management in the last 25 years. Regulatory approval of multiple drugs targeting three major pathways, *i.e.*, nitric oxide, endothelin and prostacyclin pathway by different routes of administration based on 41 randomized clinical trials, development of the combination strategies and escalation of treatment based on the patient risk status after a pre-specified period of treatment is currently accepted as standard of care.<sup>[3]</sup> Initiation of the drugs targeting one of the three different pathways is usually based on the multiple factors like physician experience, patient preferences and cost *etc.* The *de novo* use of combination therapy in PAH patients was tested in ambition trial. The study noted that use of combination therapy with Ambrisentan and Tadalafil resulted in lower risk of clinical failure events than the monotherapy.<sup>[16]</sup> Since the initial trial, the use of combination therapy with Macitentan and Sildenafil, Riociguat and Bosentan and Sildenafil and ERA or PDE-5 inhibitors have received highest recommendation as outlined in the guidelines. It is important to note that use of PDE-5 inhibitors and Riociguat is contraindicated at this time.<sup>[17-20]</sup> In cases of high risk, intravenous epoprostenol therapy receives highest recommendation as it has been shown to reduce the 3 month mortality as noted in the clinical trial.<sup>[21]</sup> In addition, in the recent years there is a shift in primary endpoint like 6 min walk distance to clinical worsening. It is important to appreciate that the drugs targeting the above three pathways have most commonly been tested in idiopathic PAH, heritable PAH, PAH due to drugs, PAH associated with corrected congenital heart disease, Eisenmenger syndrome or associated with connective tissue disease. The drugs should not be used to treat patients with PH due to heart or lung disease as the trials included strict hemodynamic criteria of PAWP of  $\leq 15$  mmHg and PA mean pressure of  $\geq 25$  mmHg and PVR of  $\geq 3$  wu. In cases of advanced disease on maximal medical therapy, lung transplant may be required if patient is deemed eligible.

## 4 Conclusions

PH complicates the course of various clinical conditions. It is associated with significant morbidity and mortality. There have been significant diagnostic and therapeutic developments in the recent years that have impacted the field. Accurate risk assessment upon diagnosis of PAH and initiating optimal PAH specific therapy in a timely manner have been shown to impact the short time survival and time to clinical worsening in the patients. Optimal treatment for other forms of PH should be contextualized within the extent of the underlying disease which is gauged by the combination of physiological, imaging and hemodynamic assessment.

## Acknowledgments

All authors had no conflicts of interest to disclose.

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