REVIEW

PULMONARY HYPERTENSION – A MINIREVIEW

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Abstract. *Pulmonary hypertension (PH) is a rare disease characterized by considerable morbidity and mortality. Significant progress has been recently achieved in enhancing the identification, diagnosis, and treatment of the disease, as evidenced by the latest guideline. Several additional medical conditions can complicate the overall understanding of the patient's condition, making the diagnosis even more difficult. Genetic and molecular factors, certain toxic drugs (such as methamphetamines, desatinib, or anorexigens), systemic disorders, or other predisposing conditions lead to the remodeling of distal pulmonary arterioles, resulting in pulmonary hypertension. Non-invasive investigations are initially undertaken in suspected cases based on cardiac biomarkers, lung function, and echocardiograms. Nowadays, the definition of pulmonary hypertension (PH) has recently changed, now including patients with mean pulmonary artery pressure >20 mmHg, and hemodynamic evaluation with right heart catheterization remains the diagnostic gold standard. Beyond new medically targeted therapies, there is a greater appreciation for the importance of supervised training in stable PH and the possible role of interventional therapies in select cases. The landscape of PH is in constant change, characterized by progress, innovation, and new medical opportunities.*

Keywords: *pulmonary hypertension, right heart catheterization, heart failure, pulmonary vascular resistance, interstitial lung disease*

DOI https://doi.org/10.56082/annalsarscimed.2023.2.12

Introduction

Pulmonary hypertension (PH) is a term used to describe a range of conditions characterized by increased average pressure in the pulmonary artery, structural alterations in the pulmonary circulation, and the development of vaso-occlusive lesions [1].

Although there are multiple etiologies for pulmonary hypertension (PH), this condition consistently exhibits worsening symptoms and heightened mortality rates, irrespective of the primary pathology. Patients often present with dyspnea on exertion and signs of right heart failure. There are five different groups of PH based on different causes, which are defined by the World Health Organization (WHO) and are referred to as PH WHO Groups. The need for an accurate diagnosis and classification of pulmonary hypertension is required, not only for reasons of prognosis but also because the medical guidance of the PH is based on the management of the underlying etiology as well as the correct medical therapy. Diagnosis requires a high index of suspicion and extensive testing to confirm the condition as well as determine the underlying etiology [1-5].

Deffinition & Classification

Pulmonary hypertension is divided into 5 clinical groups: pulmonary arterial hypertension (PAH), PH due to left-sided heart disease, PH due to chronic lung disease/ hypoxia, PH due to pulmonary artery obstruction and PH with unclear and/or multifactorial mechanisms [6,7].

Pulmonary hypertension (PH) can also be defined by a hemodynamic classification that aids in diagnosis, with measurements taken during right heart catheterization (RHC), when the patient is resting in the supine position [8,9].

A mean pulmonary arterial pressure (mPAP) of 20 mmHg or greater at rest, a pulmonary artery wedge pressure (PAWP) of 15 mmHg or less, and a pulmonary vascular resistance (PVR) of 3 Wood units (WU) or greater represent the hemodynamic criteria that are being taken into consideration for PH [8,9].

With a prevalence of 50% to 70% and 30% to 50%, respectively, left heart diseases and lung diseases are the two most prevalent subtypes of PH [10].

According to the new 2022 guidelines for PH, the 5 subtypes of PH include [6]:

1. Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

1.1.1 Vasoreactivity test non-responders

1.1.2 Acute vasoreactivity test responders

1.2 Heritable PAH.

1.3 Associated with drugs and toxins:

There is a definite association between the following drugs and PH: aminorex, benfluorex, dasatinib, dexfenfluramine, fenfluramine, menthamphetamines and toxic rapeseed oil. Furthermore, in some cases, there is a possible association between PH and the following: alkilatying agents (Cyclophosphamide, Mitomycin C), amphetamines, bosutinib, cocaine, diazoxide, indirubin, direct-acting antiviral agents against the hepatitis C virus (Sofosbuvir), interferon alpha and beta, leflunomide, L-tryptophan, phenylpropanolamine, ponatinib, selective proteasome inhibitors (carfilzomib), solvents (trichloroethylene), St John's Wort.

1.4 Associated with:

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart disease

1.4.5 Schistosomiasis

1.5 PAH with features of venous/capillary (PVOD/PCH) involvement

1.6 Persistent PH of the newborn

2. PH due to left heart disease

2.1 Heart failure:

2.1.1 with preserved ejection fraction

2.1.2 with reduced or mildly reduced ejection fraction

2.2. Valvular heart disease

2.3. Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH as a result of chronic lung disease/ hypoxia

3.1 Obstructive lung disease, or emphysema

3.2 Restrictive lung disease

3.3 Lung disease with a mixed restrictive or obstructive pattern

3.4 Hypoventilation syndromes

3.5 Hypoxia without lung disease (e.g., high altitude)

3.6 Developmental lung disorders

PH is frequently observed in patients with lung diseases such as chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease (ILD), altitude-related hypoxia, and hypoventilation syndromes, but is uncommon in patients with isolated obstructive sleep apnea [6,7].

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic pulmonary hypertension

The rising number of patients diagnosed with chronic thromboembolic pulmonary disease (CTEPD) is most likely related to a better understanding of the disease, as well as improved screening and therapy strategies [6].

4.2 Other pulmonary artery obstructions, including:

- sarcomas (high or intermediate grade, or angiosarcoma)
- other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ-cell tumors of the testis)
- non-malignant tumors (e.g., uterine leiomyoma),
- arteritis without connective tissue disease,
- congenital pulmonary arterial stenoses,
- hydatidosis.

5. PH with unclear and/or multifactorial mechanisms.

5.1. Haematological disorders: inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders

5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1

5.3 Metabolic disorders: glycogen storage diseases and Gaucher disease

5.4 Chronic renal failure with or without haemodialysis

5.5 Pulmonary tumor thrombotic microangiopathy

5.6 Fibrosing mediastinitis

Epidemiology

Despite the fact that PH epidemiology is still an area of ongoing research and additional data is required, it varies globally due to a number of factors, including genetics, topography, the environment, socioeconomic status, and socioeconomic conditions, in addition to health system deficiencies. Unfortunately, not all patients with pulmonary hypertension are referred to specialist centers that can provide proper evidence of the patient's main characteristics in a satisfactory database, which could later offer data about the prevalence and incidence [11,12].

PH affects approximately 1% of the global population and almost 10% of patients who are older than 65 years. Over time, left heart diseases and lung diseases have emerged as the most prevalent etiologies of pulmonary hypertension. However, chronic infectious diseases, hypertensive heart disease, cardiomyopathy, and rheumatic heart disease continue to be the main factors contributing to the development of PH in developing countries. Human immunodeficiency virus (HIV), a family history of portal hypertension or PAH are all potential risk factors. Chronic thromboembolic pulmonary hypertension (CTEPH) can be associated with permanent

intravascular devices, malignancy, inflammatory bowel diseases, and a history of pulmonary embolism. [4,11,13].

Clinical Features

The clinical manifestations that a patient may exhibit are generally vague and often coincide with those observed in numerous other cardio-pulmonary disorders. A family history, sexual history, and travel history are extremely important when evaluating a patient with suspected PH. Common symptoms of PH include exertional dyspnea, fatigue, weakness, angina, presyncope, and syncope [15].

On physical examination, pulmonary hypertension may manifest as a systolic murmur caused by tricuspid regurgitation, an elevated second pulmonic heart sound, or a left parasternal lift or retraction. Distension of the jugular vein accompanied by abnormal waveflow and fluid retention resulting in ankle edema or abdominal distention are concerning symptoms that typically signify the progression of pulmonary vascular disease. Rare symptoms due to enlargement of the pulmonary artery (PA) can include chest pain on exertion (due to compression of the left main coronary artery), hoarseness of voice (caused by compression of the left recurrent laryngeal nerve - Ortner syndrome), wheezing, cough, lower respiratory tract infection [4,12,15].

Paraclinical evaluation

1. Blood tests

Although blood tests are not sufficient for the diagnosis, they can show organ failure and may even differentiate some cases of PH. Routine biochemistry, hematology, liver and thyroid function tests, and NT-proBNP levels are all essential blood tests in all patients [6].

Routine screening for HIV, hepatitis, and connective tissue disease is useful. When there is high clinical suspicion, the physician should consider a panel that includes anticentromere, antitopoisomerase, anti-RNA polymerase III, double-stranded DNA, anti-Ro, anti-La, and U1-RNP antibodies and serological testing for scleroderma. This includes antinuclear antibodies (ANAs). Because ELISA can be associated with false-negative results, ANA immunofluorescence is advised and should be considered positive at a level ≥ 1:160. Conversely, when considering a thrombophilic state, such as in connective tissue diseases, it is advisable for clinicians to conduct coagulopathy and thrombophilia screenings using anticardiolipin antibodies, lupus anticoagulant, and β2-glycoprotein antibodies [6,16].

Patients with systemic sclerosis (SSc) and other inflammatory diseases may have decreased selenoprotein P and copper levels in addition to elevated ceruloplasmin levels, according to a recent study. Additional investigations are required to establish the diagnostic efficacy of these biomarkers in relation to SSc-PAH [17].

2. Electrocardiography (EKG)

Although a normal EKG does exclude PH, there are some indicators on the EKG may suggest the presence of this condition. Indicators of PH include right ventricular (RV) hypertrophy, right axis deviation on ECG, right bundle branch block, P pulmonale and QTc prolongation. RV strain is more sensitive finding in comparison to RV hypertrophy [12,15].

3. Echocardiography

Echocardiography remains the most important screening tool to estimate the probability of PH. If the ecocardiography provides evidence of PH, the diagnosis must be confirmed with RHC [18].

Tricuspid regurgitation velocity (TRV), which can be computed with consideration for right arterial pressure (RAP), is the basis for calculating the pulmonary artery systolic pressure (PASP). In order to estimate the RAP, the diameter variations of the inferior vena cava (IVC) observed during respiratory expiration and inspiration can be useful. An IVC diameter > 21 mm with < 50%

collapsibility indicates a higher RAP between 10–20 mmHg. Considering the inaccuracies in calculating RAP, peak tricuspid regurgitation velocity and additional echocardiographic signs of PH can stratify patients into low, intermediate or high probabilities of PH [18-20].

4. Right heart catheterization

Right heart catheterization represents the gold standard for diagnosing and classifying PH. It is a procedure that requires meticulousness and the performer must follow standard protocols, which has the advantage of not requiring hospitalization. Cardiac catheterization should be performed, if it is possible, in symptomatic PH patients. In some elected cases, after the PH is confirmed by the RHC, coronary angiography might be indicated [18,21].

Furthermore, left cardiac catheterization provides an additional diagnostic benefit, if feasible, for patients who may also be afflicted by advanced lung disease, mitral stenosis, or pulmonary venous hypertension [21].

5. Pulmonary function tests and ventilation/perfusion scintigraphy

Pulmonary function tests (PFTs) and analysis of arterial blood gas (ABG) are also needed in order to differentiate between PH groups, assess comorbidities, determine the need for supplementary oxygen, and last but not least, determine the severity of the disease [19].

Pulmonary function tests in patients with suspected PH should encompass forced spirometry, body plethysmography and lung diffusion capacity for carbon monoxide (DLCO). Generally, the partial pressure of arterial oxygen (PaO2) is normal or slightly reduced and the partial pressure of arterial carbon dioxide (PaCO2) is typically lower than normal due to alveolar hyperventilation. A severe reduction of PaO2 might raise suspicion for hepatic disease or other abnormalities with a right-to-left shunt, and a low PaCO2 at diagnosis is associated with a worse prognosis [19].

Guidelines recommend ventilation–perfusion (V/Q) scintigraphy or single-photon emission computed tomography (SPECT) as the imaging modality of choice to exclude CTEPH in patients with suspected or newly diagnosed PH. In the absence of parenchymal lung disease, a normal perfusion scan excludes CTEPH with a negative predicted value of 98% [22,23].

6. Cardiac magnetic resonance imaging (MRI)

Cardiac MRI is a sensitive technique for detecting the early signs of PH, detecting early right ventricle (RV) dysfunction, despite a well-preserved ejection fraction, but it is being used in selected cases due to its lack of availability and high cost. This technique reproduces with high accuracy the atrial and ventricular size, morphology, and function. Additional information on the detection of myocardial fibrosis can be assessed by using late gadolinium enhancement (LGE) imaging [18,24,25].

7. Chest computed tomography (CT)

High-resolution CT (HRCT) chest imaging is a key investigation for the evaluation of the lung parenchyma, and it can identify possible causative processes. Some of the possible features of pulmonary arterial hypertension that could be ascertained are represented by:

- central pulmonary artery dilatation;
- abrupt narrowing or tapering of peripheral pulmonary vessels;
- right ventricular hypertrophy;
- right ventricular and atrial enlargement;
- dilated bronchial arteries;
- a mosaic pattern of attenuation due to variable lung perfusion, particularly observed in chronic thromboembolic pulmonary hypertension [18,26,27].

8. Genetic testing

Genetic testing helps clinicians not only to better define the phenotype of PAH patients in order to facilitate treatment but also to correctly classify the patients. Genetic testing should encompass BMPR2 as a minimum requirement, and ideally include ACVRL1, ENG, and TBX4 as well, given their high prevalence in PH. Patients with potential genetic mutations are prone to developing PAH at a younger age. Consequently, they could present with a more compromised hemodynamic status and face an elevated likelihood of mortality or requiring a lung transplant. In selected cases, a genetic diagnosis may have a significant impact on clinical management and therapeutic strategies [28] [29].

Treatment

Although there is no drug that can cure this disease, the main goal of the treatment is to improve the quality of life by raising functional status and minimizing symptoms. Regarding the treatment of PH, five different classes of vasoactive drugs are now available:

- endothelin receptor antagonists (Ambrisentan, Bosentan, Macitentan);
- phosphodiesterase-5 inhibitors (Sildenafil, Tadalafil);
- soluble guanylate cyclase stimulators (Riociguat, Cinaciguat);
- prostanoid agents (Epoprostenol, Treprostinil, Iloprost);
- prostacyclin receptor agonists (Selexipag).

Long-term studies have provided evidence that various combinations of these compounds improve the progression-free survival of patients with pulmonary arterial hypertension. Nowadays, there are a few new agents that may revolutionize the pharmacological approach. Sotatercept, Sirolimus, Seralutinib, Imatinib and Rodatrstat ethyl are some of the new emerging therapeutic pathways in PH, with ongoing trials yet to be completed [29-31].

Fluid retention is a primary goal in the management of patients with PH and if edema develops, medication is required. In this case, it is recommended to limit the amount of fluids taken in and use diuretics like loop diuretics, thiazides, and mineralocorticoid receptor antagonists [18].

Emerging therapies for group 2 PH include sodium–glucose cotransporter 2 (SGLT2) inhibitors (Empaglifozin), glucagon-like peptide-1 agonists and angiotensin receptor neprilysin inhibitors (Sacubitril/Valsartan). The SGLT2 have shown some promise in subjects with group 2 PH [29,32].

There are three therapeutic targets that have been, for decades, the main pillars that have supported medical treatment:

- the endothelin pathway;
- the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway;
- the prostacyclin pathway. [33]

While calcium channel blockers (CCB) and endothelin receptor antagonists (ERA) inhibit vasoconstriction, soluble guanyl cyclase stimulators (sGCs), phosphodiesterase (PDE)−5 inhibitors and prostacyclin-analoga (PRA) enhance vasodilation [10].

The guidelines recommend lifelong therapeutic anticoagulation in all patients with CTEPH and pulmonary end arterectomy (PEA) is the surgical treatment of choice in this disease. Balloon pulmonary angioplasty, among the uses of Riociguat, Treprostinil s.c., or a combination therapy with soluble GC simulator/PDE5i, ERA, or parenteral prostacyclin analogue are part of the surgical and pharmacological treatment of PH that may be considered for inoperable patients. Furthermore, testing for antiphospholipid syndrome is recommended, and if confirmed, treatment with a vitamin K antagonist should be initiated [29,33].

Management of patients with underlying lung disease starts with treating of the underlying lung disease. The use of supplementary oxygen and non-invasive

ventilation might be useful, where indicated [33].

There are several subgroups of PH patients who require special attention. Firstly, drug-induced or toxin-associated PH should be suspected in patients with exposure and no other cause of PH, and immediate discontinuation of the causative agent is recommended. Iron deficiency anemia is common and should be treated in patients with PAH. If severe anemia is encountered (Hb < 7-8 g/dl), i.v. supplementation is recommended. Moreover, these patients should also be vaccinated, at least against influenza, Streptococcus pneumoniae, and SARS-CoV-2 [18,34].

Prognosis

Without medical intervention, the prognosis of idiopathic PH is unfavorable, with a life expectancy of only 2 to 3 years following diagnosis. The most important prognostic factor is right ventricular function and NYHA functional class represents another important predictor of survival, with a class IV mean survival of less than 6 months. Increased mortality is also frequently seen in pregnant patients with advanced PH. For better educational and emotional support for the patient, PH centers should inform and encourage them to join patient associations. In this order, health care provides a more efficient delivery, with a patient being totally involved in the curing process [11,18].

Conclusions

In recent years, the range of treatment options for patients with pulmonary arterial hypertension has significantly expanded. As time has passed, these options have become more targeted and effective, making the field of PH more stimulating to work in. The best treatment option for these patients has to be determined on an individual basis. Moving away from medication, we have a greater appreciation for the importance of the potential role of interventional therapies in select cases and new diagnosis pathways. Like any serious and life-threatening rare disease, pulmonary arterial hypertension must be diagnosed and treated at specialized centers. The future holds much promise thanks to the hard work and collaboration of patients, scientists, and physicians across the globe.

Author Contributions: M.I.M. conceived the original draft preparation. M.I.M. and C.C.D. were responsible for conception and design of the review. M.I.M. was responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements: *"The authors declare no conflict of interest regarding this article".*

Acknowledgments: *None.*

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