

INTRODUCTION

Pulmonary hypertension connoting high blood pressure in arteries of the lung, has been labeled an orphan disease earlier for affecting few individuals and being overlooked by medical profession. It is complex ailment with relentless course especially if untreated, heading to right heart failure and death. It is now in limelight due to exciting discoveries in understanding the disease and introduction of new pharmacotherapies. The field has moved so rapidly that it has witnessed two major guidelines in last two years. i.e., CHEST guidelines (2014) and ESC/ ERS guidelines (2015). The morbidity and mortality ascribed to it has considerably declined by virtue of current management strategies.

DEFINITION

Pulmonary hypertension (PH) broadly refers to mean pulmonary artery pressure of 25mm Hg or greater. The definition of Group 1 of PH also referred to as pulmonary artery hypertension (PAH) requires that left sided cardiac filling pressure (PAWP), Left ventricular end-diastolic pressure (LVEDP) or left atrial pressure (LAP) be 15mm Hg or less and calculated pulmonary vascular resistance (PVR) be Wood units ≥ 3 .

CLASSIFICATION

Diverse clinical groups of PH are classified into 5 groups based on pathological characteristics:

Table 1: Classification of Pulmonary Artery Hypertension (Group 1)

Idiopathic(IPAH)
Heritable
BMPR 2 mutation etc.
Drugs/ Toxin
Anorexigens (Fenfluramine)
Rapeseed
Associated with
Connective tissue disease(systematic sclerosis) HIV infection
Portal hypertension
Congenital Heart Disease
Schistosomiasis

BMPR2=Bonemarrow protein Receptor2, HIV = Human Immunodeficiency syndrome; Adapted from 2015 ESC/ERS guidelines

Group1: Pulmonary artery hypertension (PAH) predominantly affecting distal pulmonary arteries (<500 μm). The most frequent etiologies of group 1 are enlisted in table 1. It is further classified into:

Group 1: Pulmonary veno-occlusive disease

Group 1: Persistent pulmonary hypertension of the newborn

Group 2: Due to left heart disease

Group 3: Due to lung disease

Group 4: Due to chronic thromboembolic pulmonary hypertension (CTEPH)

Group 5: Due to unclear multifactorial mechanism

EPIDEMIOLOGY

PH secondary to left heart disease especially rheumatic valvular disease constitutes a major burden of PH in India and other developing countries. However, the most common etiology of PH in western world is idiopathic (iPAH) followed by associated (aPAH).

According to REVEAL Registry the prevalence of PAH in US was 12.4 cases per million and shown to affect more women than men (3.6:1) with a mean age of 47 years. In 1980's 5 year survival of PAH was 37 % but it seems to be 60% now.

CLINICAL PRESENTATION

A thorough history and examination is essential for screening, diagnosis, management and prognostication. Early in course of disease patients are asymptomatic but later they present with dyspnea, chest pain, syncope and cough. Clinical examination may reveal accentuated pulmonary component of second heart sound (S2) with narrow spilt, holosystolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary regurgitation. Signs of congestive heart failure are noted in late stage.

DIAGNOSTIC WORKUP

- PH/ PAH risk factors and clinical picture
- Echocardiography, Skigram, ECG, pulmonary function tests, diffusion capacity of lungs for carbon monoxide(DLCO), HRCT, V/ Q scan and arterial blood gases
- Right heart catheterization
- Specific Diagnostic tests for PAH associated diseases

Table 2. World Health Organization Functional Classification of Patients with Pulmonary Hypertension

Classification	Physical Activity	Symptoms Dyspnea, fatigue, chest pain syncope
Class I	No limitation	None upon ordinary physical activity
Class II	Slight limitation	Symptoms appear upon less than ordinary activity
Class III	Marked limitation	Symptoms appear upon less than ordinary activity
Class IV	Severe limitation	Symptoms appear upon any physical activity or may be present at rest; signs of right heart failure present

Adapted from CHEST guidelines and expert panel Report (2015)

e. Biomarkers like BNP and NT-Pro BNP

FUNCTIONAL CLASSIFICATION

WHO Functional Classification (table 2) is the commonest tool used to assess impact of disease and efficacy of treatment. WHO functional class (FC) III and IV have a poorer prognosis. 6 minute walk distance (6MWD) also is a useful parameter to identify high risk subject and treatment benefits.

RISK STRATIFICATION

It is vital to plan treatment options and categorize patients to low, moderate and intermediate risk categories. Patient with right heart failure, rapid symptom progression, recurrent syncope, FC IV and 6 min walk distance <165 meters fall in high risk category. Cardiopulmonary exercise testing, serum markers BNP (>300ng/L) and NT -proBNP(>1400ng/L) echocardiography (RA >26cm, pericardial effusion), hemodynamics (RAP> 14mm Hg, cardiac Index < 2.L/min/m²) and mixed venous oxygen saturation ≤60% predict severe form of disease.

TREATMENT STRATEGIES

Timely treatment of left heart disease, congenital heart disease, respiratory ailments and avoiding offending drugs can prevent development of PH.

Oxygen therapy is a pulmonary vasodilator and hence useful especially in hypoxemic. Role of anticoagulation is controversial as conclusive randomized data is lacking. Exercise rehabilitation and vaccination to prevention respiratory infection are needed.

Vascular directed therapies

They are the corner stone of treatment of PAH today and have established their role in last few decades. There are four different categories based on separate mechanisms & targets.

a. Calcium channel blockers(CCBs)

Previously widely accepted as a vasodilator therapy in 1980's, now the only use is in patients who show vasoreactivity during right heart catheterization and hemodynamic lowering of pulmonary arterial pressure by ≥ 10mm Hg

b. Prostacyclin Pathway (Prostanoids)

They are the mainstay of therapy for those

with advanced disease or in whom worsening continue to occur despite other drugs. In PAH prostacyclin levels are reduced owing to downregulation of prostacyclin synthetase and prostacyclin analogues stimulate this pathway. Available agents are intravenous(epoprostenol and trepostinil), subcutaneous and oral(eprostenil) and inhaled(ilprost). Limitations in India are high cost and non-availability. Side effects include flushing, headache, jaw pain and diarrhea. Selexipeg is a potent orally available selective prostacyclin PG-12 receptor agonist. The high selectivity offers improved tolerability. In the double blind placebo-controlled, multicentric GRIPHON study on 1150 patients, the addition of oral selexipeg led on to morbidity/ mortality events reduction by 39% as compared to placebo.

c. Nitric oxide (NO)Pathway

Endothelium derived NO induces vasodilation in pulmonary vasculature, smooth muscle cells and inhibits proliferation and acts through secondary messenger (cyclic Guanosine Monophosphate). The drugs in this category include:

Phosphodiesterase-5 Inhibitors

Sildenafil (20mg TDS) or tadalafil(20-40mg/day) are available in India. Their use as mono- and combination therapy has been substantiated. Vardenafil (5-10mg/day) also belongs to this category. Common side effects are headache, flushing, nasal congestion & hypotension when used with nitrates.

Riociguat is a unique drug in this category as it acts on soluble Guanyl Cyclase and it is a sensitizer to endogenous NO. It can be added to improve Functional Class and in treatment of CTEPH, when the case is inoperable or with failed surgical thromboendarctectomy. Efficacy and safety of riociguat (2.5mg) is proven with sustained improvement in exercise capacity upto 1 year. Rarely hemoptysis occurs with its use.

d. Endothelin receptor antagonists (ERA)

They nullify the effect of endothelin in causing vasoconstriction and proliferation of smooth

muscles. Bosentan binds to A and B endothelin receptors. Initially 62.5mg b.i.d is given for a month followed by 125mg b.i.d. Hepatotoxicity can lead to discontinuation. Fluid retention, anemia and oligospermia can also occur rarely. Ambrisentan, is first nonsulfonamide ERA. 5-10mg single dose is given after titration. Both these drugs are available in India can improve Functional Class. Macitentan, the new oral ERA has shown superior efficacy as compared to bosentan and ambrisentan. The phase III SERAPHIN study has shown reduction in morbidity and mortality over 3.5 years. (thus not focusing only on functional end-points alone for other drugs.)

NOVEL DRUG TARGETS

Other drugs under investigation include tyrosine kinase inhibitor Imatinib (400mg/day) to suppress platelet derived growth factor (PDGF), serotonin pathway inhibitors (terguride), Rho-kinase inhibitors and vasoactive intestinal peptide also hold some promise.

UPFRONT COMBINATION THERAPY

Currently the understanding is that the more aggressive use of combination therapy initially in FC II & III rather than monotherapy may benefit patients. AMBITION trial on 500 patients has suggested that the combination of tadalafil and ambrisentan is superior to monotherapy in reducing clinical failure events in this category. Triple combination therapy with intravenous epoprostenol, bosentan and sildenafil in FC III or IV patients has been shown to improve 6 MWD and hemodynamics. ESC/ERC 2015 guidelines have strongly recommended combination therapy in FC II or III whereas it was not so in earlier guidelines.

OTHER TREATMENT MODALITIES

Pulmonary thromboendarctectomy is emerging as treatment of choice in CTEPH patients but it is not effective if distal vasculopathy is there. Pulmonary artery vascular interventions and denervation continue to be therapeutic target in selected patients.

Stem cell therapy and gene modulation of (BMPR 2) mutation is being investigated.

Heart lung transplant continues to be the option in patients not responding to other measures with 5 year survival of 47%.

SPECIFIC SITUATIONS

In PH due to left heart disease, there is need to address to associated co-morbidities. A special situation mimicking PAH is heart failure with preserved ejection fraction but here the role of PAH specific drugs is not validated.

PH secondary to pulmonary disease is usually slowly progressive and mostly mortality is due to respiratory pathology. Whether pulmonary hypertension treatment changes outcome in these patients is a matter of debate and it should be considered only in those with severe PH or a circulatory impairment. In pregnancy the best option in PAH patients is to avoid it as it carries very high mortality and only anecdotal experience with specific

drugs is there. Advanced PAH targeted therapy has shown to improve survival in Eisenmenger's syndrome both as monotherapy and as combination therapy.

CONCLUSION

Deeper insight into mechanism of PAH, vascular directed therapies, evidence-based guidelines and other recent advances have been able to convert a "potential killer" to a "chronic disease". Early screening, accurate diagnosis, prognostication and optimised treatment is instrumental for this change. Treatment options of PH with chronic heart and parenchymal lung disease need to be addressed. Upfront combination therapy is emerging as a sound option in selected cases FC II or III but its superiority to monotherapy followed by stepped up care is not fully established. Low/intermediate risk patients deserve special attention considering the cost and side effects of multiple drugs. All the controversial issues and gaps can only be addressed to by quality clinical trials in the future.

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