Review Article

Pulmonary Hypertension

Manish Kumar[1], D P Singh[2]

Pulmonary hypertension (PH) is a spectrum of diseases that involves lung vasculature (pulmonary artery, pulmonary vein and capillaries). The patient may present with clinical features of dypnea, chest pain and syncope. The classification is based on the site of vasculature involved and accompanying cardiorespiratory conditions. PH should be suspected in patients with new onset unexplained exertional dyspnea. Echocardiography is a vital screening tool. Right heart catheterization is needed for definitive diagnosis. Inspite of significant advancement in the understanding of pathophysiology of PH, vasodilator therapy remains the main cornerstone of treatment. [*J Indian Med Assoc* 2019; **117:** 40-3 & 58]

Key words **: Pulmonary hypertension, Idiopathic pulmonary hypertension, Chronic thoromboembolic pulmonary hypertension.**

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP) $\geq$ 25 mmHg at rest as assessed by right heart catheterization[1,2]. PH can be found in multiple clinical conditions. It is a progressive, fatal disease if untreated, although the rate of progression is highly variable.

Clinical Presentation :

Pulmonary hypertension often presents with nonspecific symptoms. These symptoms are often difficult to dissociate from those caused by a known underlying pulmonary or cardiac disorder. The most common symptoms—exertional dyspnea, fatigue and syncope—reflect an inability to increase cardiac output during activity. Typical angina may occur despite normal coronary arteries. The mechanism is unclear, but anginal chest pain may be due to pulmonary artery stretching or right ventricular ischemia. Hemoptysis resulting from the rupture of distended pulmonary vessels is a rare but potentially devastating event[3,4].

Updated clinical classification of pulmonary hypertension (PH)[2,5]:

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH 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 long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

Diagnostic Evaluation :

A high index of suspicion, a meticulous history and a careful physical examination are very important in the diagnosis of pulmonary hypertension. Particular attention should be given to previous medical conditions, drug use and family history.

Department of Cardiology, Arc Hospital, Bhagalpur 812001
[1]MD (Med), DTM&H (UK), FICP, Consultant Cardiologist and Corresponding author
[2]MD, DTCD, FICP, FACP, FIAMS, FCSI, FICS, FRCP (Glasgow), Professor and Head, Department of Respiratory Medicine, Jawahar Lal Nehru Medical College, Bhagalpur 812001

In pulmonary hypertension, the ECG may demonstrate signs of right ventricular hypertrophy, such as tall right precordial R waves, right axis deviation and right ventricular strain. The higher the pulmonary artery pressure, the more sensitive is the ECG[6].

The chest x ray may show evidence of underlying lung disease. Sometimes recognition of pulmonary hypertension begins with the discovery of right ventricular hypertrophy on the ECG or prominent pulmonary arteries on the chest radiograph.

Patients with signs, symptoms or ECG or X Ray findings suggestive of pulmonary hypertension should undergo two-dimensional echocardiography with Doppler flow studies. Echocardiography is the most useful imaging modality for detecting pulmonary hypertension and excluding underlying cardiac disease. Confirmation of pulmonary hypertension is based on identification of tricuspid regurgitation. The addition of mean right atrial pressure to the peak tricuspid jet velocity gives an accurate noninvasive estimate of peak pulmonary pressure. Right ventricular dilatation and hypertrophy are late findings.

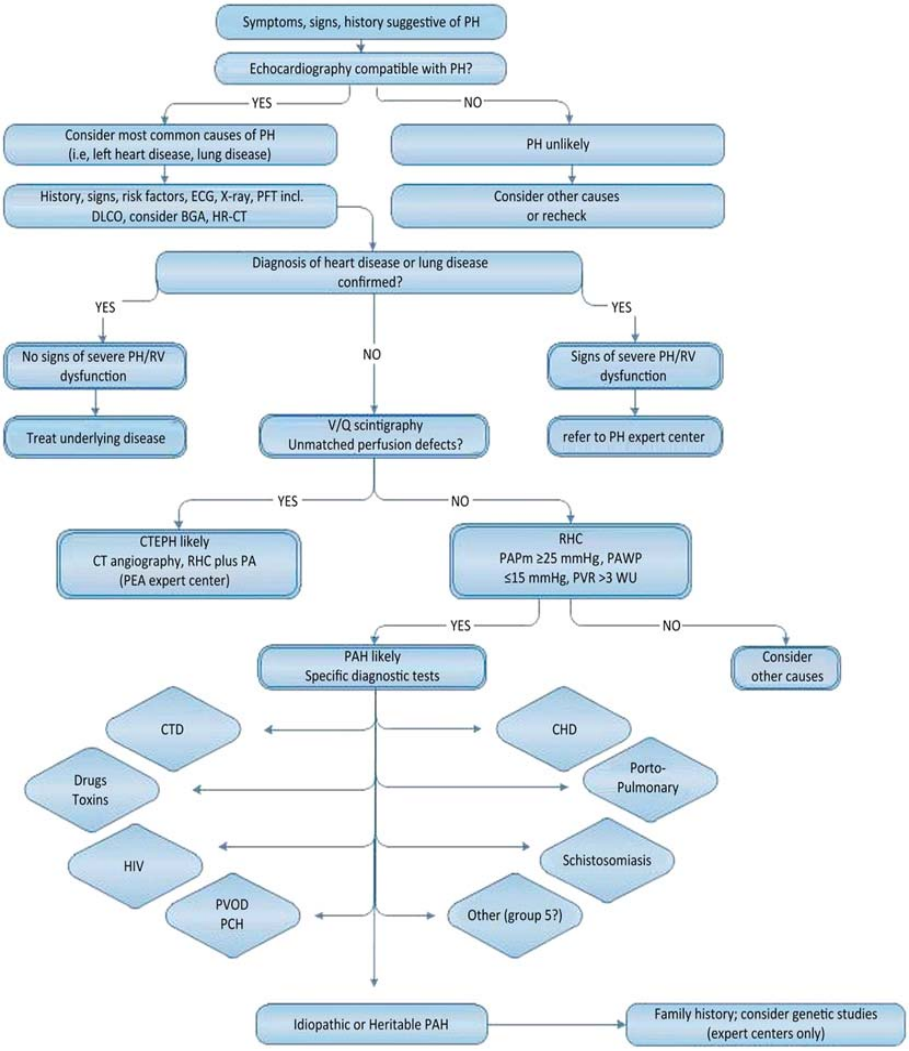

Fig 1

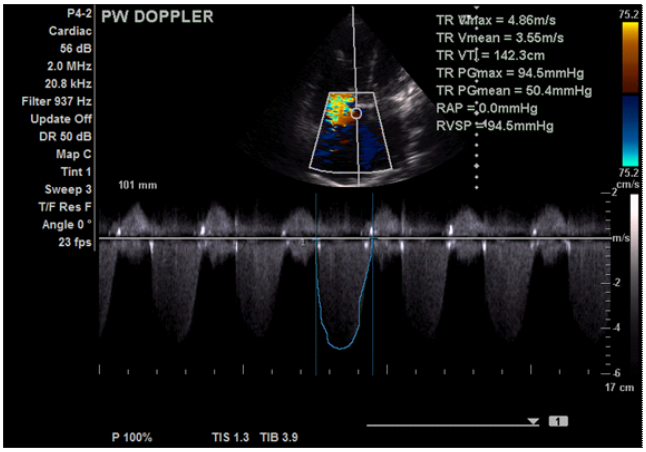

Fig 2

Figs 1 & 2 — A Case of Rheumatic Mitral stenosis with dilated RA/RV/LA, moderate TR, and PA pressure of 94 mmHg as assessed by Colour Doppler echocardiography

All patients with documented pulmonary hypertension should undergo a comprehensive laboratory evaluation to clarify the etiology. The goal is to identify or exclude treatable causes. Initial tests include complete blood count, prothrombin time, partial thromboplastin time, hepatic profile and HIV testing if needed. A hypercoagulable state should be ruled out by measuring protein C and S levels, lupus anticoagulant and D dimer.

Right Heart Catheterization remains an essential tool for the diagnostic workup of patients with PH (Figs 1-4).

Arterial blood gas analysis should be performed to exclude hypoxia and acidosis as contributors to pulmonary hypertension.

Pulmonary function tests are necessary to establish airflow obstruction or restrictive pulmonary pathology. Unless hypoxia is present, pulmonary hypertension cannot

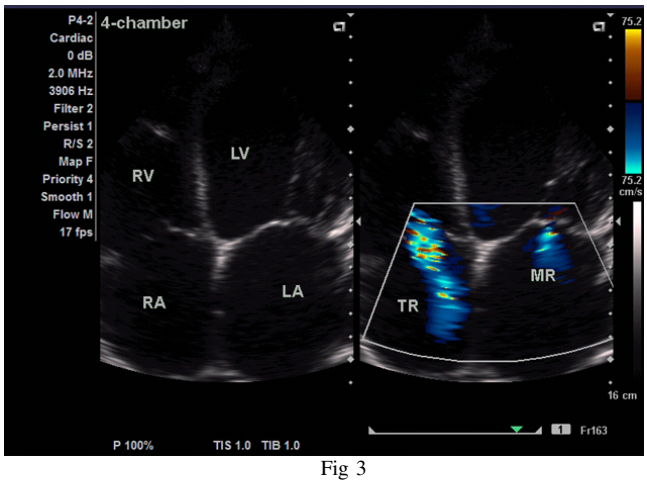

Fig 3

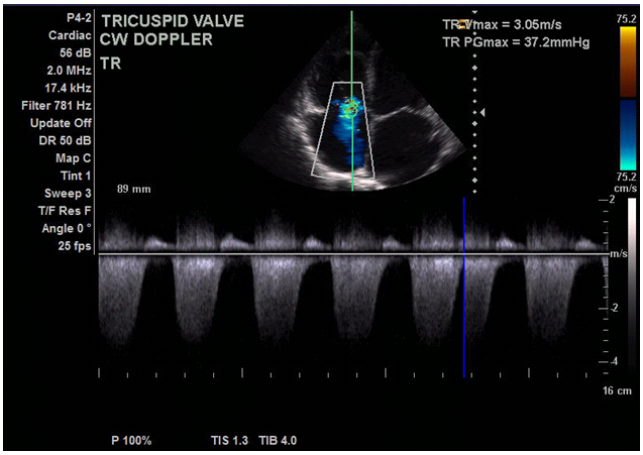

Fig 4

Figs 3 & 4 — A case of dilated cardiomyopathy with TR/ MR and PA pressure of 37 mm Hg

be attributed to these disorders until pulmonary function is severely reduced.

If the cause of the pulmonary hypertension remains unexplained, chronic thromboembolism should be excluded before the diagnosis of primary pulmonary hypertension is accepted. Ventilation-perfusion lung scanning is a reliable method for differentiating chronic thromboembolism from primary pulmonary hypertension. The finding of one or more segmental or larger perfusion defects is a sensitive marker of embolic obstruction. In primary pulmonary hypertension, the ventilation-perfusion scan is normal or demonstrates patchy subsegmental abnormalities.

If the ventilation-perfusion scan suggests the presence of chronic thromboembolism, pulmonary angiography can be performed safely to confirm the diagnosis, define the extent of disease and evaluate the need for surgical thromboendarterectomy.

Early identification and treatment of pulmonary hypertension (PH) is generally suggested because advanced disease may be less responsive to therapy. Treatment begins with a baseline assessment of disease severity, followed by primary therapy. Primary therapy is directed at the underlying cause of the PH.

Some patients progress to advanced therapy, which is therapy directed at the PH itself, rather than the underlying cause of the PH

Baseline Assessment — The baseline severity of PH should be determined prior to the initiation of therapy. This assessment is essential because the response to therapy will be measured as the change from baseline.

Pulmonary artery systolic pressure and right ventricular function can be estimated by echocardiography, and then used to make a presumptive diagnosis of PH. Right heart catheterization must be performed to accurately measure the hemodynamic parameters and confirm that PH exists. However, it is often deferred until advanced therapy is indicated because it is an invasive procedure.

Primary Therapy — Primary therapy refers to treatment that is directed at the underlying cause of the PH. It is needed in nearly all patients with PH. The disease severity should be reassessed following primary therapy, in order to determine whether advanced therapy is indicated.

Group 1 PAH — Patients with group 1 pulmonary arterial hypertension (PAH) have idiopathic pulmonary arterial hypertension (IPAH, formerly called primary pulmonary hypertension), hereditary PAH, or PAH due to diseases that localize to small pulmonary arterioles, such as connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, and drug use There are no effective primary therapies for most types of group 1 PAH. As a result, advanced therapy is often needed[8].

Group 2 PH — Patients with group 2 PH have PH secondary to left heart disease with chronic left atrial and pulmonary venous hypertension, including systolic dysfunction, diastolic dysfunction, and valvular heart disease.

Primary therapy for group 2 PH consists of treatment of the underlying heart disease

Group 3 PH — Patients with group 3 PH have PH secondary to various causes of hypoxemia, such as COPD, interstitial lung disease, other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing, or alveolar hypoventilation disorders.

Primary therapy for group 3 PH consists of treatment of the underlying cause of hypoxemia and correction of the hypoxemia with supplemental oxygen. Oxygen is the only modality with proven mortality benefit in some patients with group 3 PH. This has been established by two large trials studying patients with COPD, the most common cause of group 3 PH. Continuous oxygen therapy improves survival in patients with COPD and a PaO2 below 55 mmHg.

***Group 4 PH* —** Patients with group 4 PH have PH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature (eg, chronic thromboembolic disease)

Anticoagulation is primary medical therapy for patients with group 4 PH. Clinical evidence suggests that anticoagulation prevents recurrent pulmonary embolism.

Surgical thromboendarterectomy is primary surgical therapy for selected patients with thromboembolic obstruction of the proximal pulmonary arteries.

***Group 5 PH* —** Group 5 PH is uncommon and includes PH with unclear multifactorial mechanisms. Examples include PH caused by hematologic disorders (eg, myeloproliferative disorders), systemic disorders (eg, sarcoidosis), metabolic disorders (eg, glycogen storage disease) etc.

All groups — Several therapies should be considered in all patients with PH. They include diuretic, oxygen, anticoagulant, and digoxin therapy, as well as exercise.

Diuretics — Diuretics are used to treat fluid retention due to PH because diuresis will diminish hepatic congestion and peripheral edema. However, they should be administered with caution to avoid decreased cardiac output (due to decreased right and/or left ventricular preload), arrhythmias induced by hypokalemia, and metabolic alkalosis.

Oxygen therapy — Continuous oxygen administration remains the cornerstone of therapy in patients with group 3 PH. Oxygen should be considered for all patients with PH plus hypoxemia. The flow of oxygen needed to correct hypoxemia should be determined by measurement of the oxygen saturation. Oxygen is generally administered at 1 to 4 L/min via nasal prongs and adjusted to maintain the oxygen saturation above 90 percent at rest and, if possible, with exercise and sleep.

Supplemental oxygen will not significantly improve the oxygen saturation of patients who have congenital heart disease with a right-to-left shunt (Eisenmenger physiology).

Anticoagulation — Patients with PH are at increased risk for intrapulmonary thrombosis and thromboembolism, due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis, and a sedentary lifestyle. Even a small thrombus can produce hemodynamic deterioration in a patient with a compromised pulmonary vascular bed.

The anticoagulant of choice is warfarin, with a therapeutic goal of an International Normalized Ratio (INR) of approximately two.

Digoxin — Digoxin therapy has been shown to have both beneficial effects and drawbacks:

- Digoxin improves the right ventricular ejection fraction of patients with group 3 PH due to COPD and biventricular failure. However, these patients may be more sensitive than most patients to digitalis toxicity and require close monitoring.
- Digoxin helps control the heart rate of patients who have supraventricular tachycardias associated with right ventricular dysfunction. Verapamil is preferred for multifocal atrial tachycardia, unless there is concurrent left ventricular failure.

Exercise — Exercise training appears to be beneficial for patients with PH.

***Advanced Therapy* —** Advanced therapy is directed at the PH itself, rather than the underlying cause of the PH. It includes treatment with prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or, rarely, certain calcium channel blockers.[9]

Patient selection — Advanced therapy is considered for patients who have evidence of persistent PH and a World Health Organization (WHO) functional class II, III, or IV despite adequate primary therapy.

Endothelin Receptor Antagonists — The non selective endothelin receptor antagonist Bosentan is an approved treatment of PAH for patients who are NYHA functional lasses III & IV. Therapy is initiated at 62.5 mg BD for first month and 125 mg BD thereafter. LFT should be monitored throughout the treatment duration.

Phospodiesterase 5 Inhibitors — Sildenafil is approved for patients with functional class II & III. The recommended dose is 20 mg TID. The most common side effect is headache.

Prostacyclins — These include Iloprost, Epoprostenal & Treprostinil.

Prognosis :

The median duration of survival after the diagnosis of primary pulmonary hypertension is 2.8 years according to a study, but this figure is highly variable. As a result of new treatments, patients without hemodynamic evidence of right ventricular dysfunction may survive for more than 10 years.

The prognosis for patients with secondary pulmonary hypertension depends on the underlying disease, as well as right ventricular function. For instance, patients with COPD and moderate airflow obstruction have a three-year mortality rate of 50 percent after the onset of right ventricular failure. Survival is similarly influenced in patients with interstitial lung disease and pulmonary hypertension.

Conclusion :

Data from all over the world indicates that the majority of patients are still diagnosed at later stages of the disease, and this is not expected to change in the near future. However an early diagnosis with high index of clinical suspicion and optimal use of diagnostic tools will definitely

(Continued on page 58)

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improve the outcome of this disease.

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