Review Article

Treatment of Pulmonary Hypertension- An Overview

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Pulmonary Hypertension (PH) has been defned as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterisation (RHC)[1]. It is characterised by progressive and sustained increase in pulmonary vascular resistance, that will eventually lead to right ventricular failure. It is a life threatening condition if not treated. It mainly involves the small pulmonary arteries and results in unregulated vasoconstriction, vascular smooth muscle cell proliferation and vascular remodelling.

The common causes of pulmonary hypertension are left heart diseases and lung diseases. But significant research in the field of pulmonary hypertension has been done in pulmonary arterial hypertension (PAH) group and the new treatment options that is available now is mainly recommended for this group.

Classification

World Health Organisation classifies pulmonary hyper tension into 5 group based on pathological, pathophysiological and therapeutic characteristics. The classification that is followed now is the Dana Point classification of 2008[2]. Patients in group I are categorised as pulmonary arterial hypertension, while the remaining four groups are categorised as pulmonary hypertension.

Epidemiology

The reported prevalence of PAH from pulmonary hypertension registries is 15 cases/ million adult population[3].Idiopathic Pulmonary Arterial Hypertension(IPAH) is even rare with a frequency of 1-2 cases/million population[4]. Any age group can be affected, but IPAH is more common in females in the third decade of life and in males in the fourth decade of life.

The prevalence of pulmonary hypertension in advanced COPD is 50.2% in a study done in France among patients waiting for lung volume reduction surgery, and is usually of mild severity[5]. Up to 32% of patients with advanced idiopathic pulmonary fibrosis have PH[6]. Studies have shown that patients with combined pulmonary fibrosis and emphysema (CPFE) have higher prevalence of pulmonary hypertension[7].

Table 1: Updated clinical classifcation of pulmonary hypertension (Dana Point, 2008)

1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

1.2 Heritable 1.2.1 BMPR2, 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia) 1.2.3 Unknown

1.3 Drugs and toxins induced

1.4 Associated with (APAH) 1.4.1 Connective tissue diseases 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.4.6 Chronic haemolytic anaemia

1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease

2.1 Systolic dysfunction

2.2 Diastolic dysfunction

2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/ or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension(CTEPH)

5 PH with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: myeloproliferative disorders,splenectomy.

5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis,lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 Activin Receptor like Kinase 1 gene,

BMPR2- Bone Morphogenetic Protein Receptor, type2, APAH-Associated Pulmonary Arterial Hypertension

Pathogenesis

Pathogenesis of pulmonary hypetension is multifactorial, and not fully understood. The normal pulmonary circulation is a low resistance system which can accommodate the entire cardiac output. This is done by dilation of the existing vasculature and recruitment of unused vessels.

Endothelial dysfunction plays a key role in the pathogenesis of pulmonary hypertension. The key mediators produced by pulmonary endothelium that play a significant role in pulmonary hypertension pathogenesis are endothelin, prostacyclin and nitric oxide (NO). Prostacyclin and nitric oxide are pulmonary vasodilators and endothelin is a pulmonary vasoconstrictor. An imbalance between vasodilators and vasoconstrictors is a key contributor to the initiation and progression of the disease. The present day targeted treatment of pulmonary hypertension acts by modifying this vasoconstrictor- vasodilator mechanism.

The other proposed mechanisms of pulmonary hypertension are increased production of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and serotonin produced by platelets[8].

Pulmonary vascular resistance is increased by three mechanisms. These are vasoconstriction, remodelling of the pulmonary vessel and thrombosis in situ.

The development of pulmonary hypertension in lung disease is also due to multiple mechanisms. The commonly described mechanisms are hpoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of pulmonary vascular bed, inflammation and toxic effects of cigarette smoke. As in all the other groups of PH, an imbalance between the endothelium derived vasoconstrictors and vasodilators has also been proposed.

"Out of proportion" pulmonary hypertension

Out of proportion pulmonary hypertension is defined as an unjustified degree of pulmonary hypertension that occurs in patients with chronic lung disease. Some patients with minor pulmonary impairment in pulmonary function tests and CT thorax , were found to have high pulmonary artery pressure. This could not be solely explained by hypoxia or loss of pulmonary vascular bed. An arbitrary value of > 35mm Hg mean pulmonary artery pressure has been used to define out of proportion PH[9].

Diagnosis

Evaluation of a patient with suspected pulmonary hypertension includes investigations to confirm the diagnosis

and to find out the group to which the patient belongs. The symptoms of pulmonary hypertension are nonspecific and include breathlessness, fatigue, weakness, angina and syncope. The physical signs are left parasternal heave, an accentuated pulmonic component of second heart sound, a pan systolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary insufficiency.

The common investigations that are done include electrocardiogram, echocardiography and right heart catheterisation to confirm the diagnosis. The other investigations that may be done to classify and find out the etiology of pulmonary hypertension include chest radiography, pulmonary function testing including spirometry, DLCO and blood gas analysis; ventilation perfusion lung scan, high resolution computed tomography, contrast enhanced CT of thorax and pulmonary angiography. The other investigations that may be done for etiological diagnosis are abdominal ultrasonogram to detect portal hypertension; blood tests and immunology to detect connective tissue disorders, HIV infection and hepatitis.

Treatment

In the past few years treatment of pulmonary hypertension has undergone tremendous improvement, with many new drugs being approved for treatment. Regardless of the etiology of pulmonary hypertension, general supportive treatment is similar for all patients. Supportive treatment is aimed at improving symptoms and quality of life. The basic treatment of group2,3,4, and 5 pulmonary hypertension includes treatment of the primary disease. Specific therapy or advanced therapy is directed at the pulmonary hypertension itself, rather than the underlying cause of pulmonary hypertension. The drugs available for specific therapy includes prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors and rarely calcium channel blockers. But currently

Table 2 : Functional classifcation of pulmonary hypertension modifed after the New York Heart Association functional classifcation according to WHO

Class I	Patients with pulmonary hypertension but without resultinglimitation ofphysical activity. Ordinaryphysical activitydoesnotcauseunduedyspnoeaorfatigue,chest pain, or near syncope.
Class II.	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carryoutany physicalactivity withoutsymptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

specific pulmonary vasodilators which mainly target endothelial dysfunction in pulmonary hypertension, have been proven beneficial in group I PH only.

Assessment of therapy

The baseline assessment of severity should be done prior to starting treatment. This is essential because the response to therapy is measured as the change from baseline. Disease severity is evaluated by assessing functional impairment and hemodynamic derangement. Objective evaluation of functional impairment includes a 6 minute walk test (6MWT) and the WHO functional class (WHO-FC)[10]. Pulmonary artery systolic pressure and right ventricular function is estimated by echocardiography and right heart catheterisation.

General supportive treatment

General supportive measures of treatment are common for all groups of patients.

Physical activity : Heavy physical activity should be avoided in patients with PH, as this can lead to severe breathlessness, exertional dizziness and chest pain. Patients should be encouraged to go for physical activity within symptom limits. Exercise training appears to be beneficial as this prevents physical deconditioning and muscular atrophy.

Pregancy: Pregnancy results in increase in cardiac output and blood volume. The ability of the heart to accommodate the increased cardiovascular load is limited in patients with pulmonary hypertension. Pregnancy is associated with 30-56% mortality in patients with PAH, and so PAH is a contraindication for pregnancy[11].

Travel: Patients with WHO-FC III and IV, and those with arterial PaO2 below 60mmHg should be advised to receive supplemental oxygen during flight travel.

Prevention of infection: Patients with PAH are susceptible to develop pneumonia and it can be the cause of death in up to 7% of patients[12]. So pulmonary infections should be promptly diagnosed and treated. Vaccination against influenza and pneumococcal pneumonia is recommended.

Oral anticoagulants: Patients with PH are at increased risk of intrapulmonary thrombosis and thromboembolism. Other risk factors for the development of thrombosis include heart failure, dilated heart chambers and immobility. Definite recommendation for oral anticoagulants is for patients with IPAH, heritable PAH, drug induced PAH and group 4 pulmonary hypertension. Preferred drug for oral anticoagulation is warfarin , with a therapeutic goal of international normalised ratio (INR) of 2-3.

Supplemental oxygen: Long term oxygen therapy (LTOT) is the cornerstone of treatment for patients with group 3 PH. As hypoxemia can aggravate pulmonary hypertension by increasing pulmonary vasoconstriction , supplemental oxygen should be considered for all patients with severe hypoxemia[13].

Digoxin : In patients with right heart failure secondary to pulmonary hypertension, myocardial contractility may improve with cardiac gylcosides. But the only definite indication for digoxin therapy is the presence of supraventricular tachyarrhythmia like atrial flutter or fibrillation to slow down the ventricular rate. As most of these patients have hypoxemia and diueretic induced hypokalemia , digoxin toxicity is more likely in these group of patients.

Diuretics: Diuretics improve the symptoms and signs of right hear failure. Dose can be modified based on individual patient requirement.

Primary therapy

Primary therapy is directed at the underlying cause of pulmonary hypertension. In case of group I (PAH), there is no effective primary therapy, as the definite cause of pulmonary hypertension is not known in majority of patients. Group 2 patients develop pulmonary hypertension secondary to left heart disease. Primary therapy of the underlying heart disease is the best option available for this group of patients. Group 3 patients includes patients with lung disease and/ or hypoxia. Primary therapy consists of treating the underlying lung disease and correction of hypoxemia with supplemental oxygen. Long term oxygen therapy is the only treatment available for this group of patients with proven mortality benefit.

Patients with group 4 PH have pulmonary hypertension secondary to thromboembolic occlusion of

the pulmonary vasculature. Anticoagulants is the primary medical therapy available for this group of patients aimed at preventing recurrent pulmonary embolism. Surgical thromboendarterectomy is the definite treatment modality for selected patients with thromboembolic obstruction of the proximal pulmonary arteries. In group 5 patients primary treatment is directed against the underlying cause of pulmonary hypertension.

Specific therapy

Specific therapy is directed against pulmonary hypertension and not against the underlying cause of pulmonary hypertension. Three major groups of drugs are available for specific therapy. These are prostanoids, endothelial receptor antagonists and phosphodiesterase -5 inhibitors. Calcium channel blockers were used for the treatment of pulmonary hypertension even before the present group of targeted drugs were approved. Specific therapy is the only available treatment modality for patients with group I PH as primary therapy is not available for this group. But treatment of patients with pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis with vasodilators can result in pulmonary oedema and should be used with caution[14].

In group 2 patients advanced therapy should be avoided if possible. For group 3 patients, present guidelines do not favour specific therapy except in the context of clinical trials. Specific therapy may also be tried for those patients who remain WHO-FC III or IV in spite of treatment of underlying lung disease and oxygen therapy, especially if the severity of PH is out of proportion to the severity of lung disease . These vasodilators will reduce pulmonary artery pressure, but can worsen ventilation perfusion mismatch. Vasodilators can inhibit hypoxic pulmonary vasoconstriction especially in group 3 patients. So specific therapy can be given to this group of patients only under close monitoring.

In group 4 patients also specific therapy may be considered for those patients who remain in WHO FC III or IV in spite of anticoagulation and thromboendarterectomy.

Calcium channel blockers(CCB): Pulmonary vasoconstriction plays a significant role in the pathogenesis of pulmonary hypertension. So vasodilators like calcium channel blockers has been used for the treatment of pulmonary hypertension. The CCBs that have been commonly used are nifedipine and diltiazem. The recommended dosages are very high. Nifedipine is given in the dose of 90-180mg/day (upto240mg) and diltiazem is given in the dose of 240-720mg/day (up to 900mg). Systemic hypotension and limb oedema can occur at these dose. CCBs should be used only when there is positive vasodilator response. Agents used for vasoreactivity testing are nitric oxide, intravenous epoprostenol or intravenous adenosine. A positive acute response is defined as a reduction in mean pulmonary artery pressure of $\geq$ 10mmHg or an absolute value of mean pulmonary artery pressure $\leq$ 40mmHg with an increased or unchanged cardiac output. Generally only about 10% of IPAH patients show a positive acute vasoreactive response. But even with a positive response, only half of them show a positive long term response to CCBs. Acute vasoreactivity testing is not recommended in clinical groups 2,3,4 and5[1]

Prostanoids

Prostacyclin is a natural prostanoid produced by vascular endothelial cells and its level is found to be reduced in pulmonary hypertension. It is a potent vasodilator, inhibits platelet aggregation and has antiproliferative action.

Epoprostenol: is a synthetic prostacyclin and is available as a freeze dried preparation. It has a short half life of 3-5 minutes and should be administered as continuous intravenous infusion with an infusion pump. The dose varies from 20-40ng/kg/min. It is reserved for patients with severe PH especially those with IPAH. The common side effects include headache, flushing, jaw pain, diarrhoea and vomiting. More serious complications are infusion pump and catheter related including bleeding, site infection, bacteremia and sepsis.

Iloprost : Iloprost is a chemically stable prostacyclin analogue available for oral, intravenous and inhaled use. Being available for inhaled route is attractive as it avoids

the systemic effects of the drug.

Beraprost sodium : It is the first biologically stable oral prostacyclin analogue available for treatment of pulmonary hypertension.

Trepostinil: It is another analogue of prostacyclin which is stable at room temperature. It can be given by both intravenous and subcutaneous route. This is approved for treatment of class II, III and IV patients with PAH.

Endothelin receptor antagonists

Increased level of endothelin-1 has been seen in plasma and lung tissue of patients with pulmonary hypertension[15]. Endothelin is a vasoconstrictor and mitogen for vascular smooth muscle. It acts by binding to ETA and ETB receptors. ETA receptor stimulation results in vasoconstriction and vascular smooth muscle cell proliferation and ETB receptor stimulation results in vasodilation and it has antiproliferative action[16].

Bosentan: Bosentan is an orally active dual (ETA and ETB) endothelin receptor antagonist. It is the first molecule of this group available for treatment of pulmonary hypertension. In the BREATHE 1 trial of bosentan 213 patients with PAH with WHO FC III and IV were randomised to receive either placebo or 62.5 mg of bosentan twice daily for 4 weeks. After that bosentan was given in the dose of 125mg or 250mg twice daily for 12 weeks. After 16 weeks there was an increase in 6 minute walk distance of 44m compared to placebo. An improvement in Borg dyspnoea index and WHO FC was also seen[17].

In the EARLY trial, PAH patients with WHO FC II were given either bosentan or placebo. In this study also there was a significant reduction of pulmonary vascular resistance in patients treated with bosentan[18].

Increase in aminotransferase has been seen in patients treated with bosentan . So monthly liver function test monitoring should be done in patients receiving bosentan.

Ambrisentan: Ambrisentan is a selective ETAreceptor blocker and it has the advantage of once daily administration. In ARIES 1(5or 10mg) and ARIES 2 (2.5 or 5mg) trial patients with PAH were randomised to receive ambrisentan or placebo orally once daily for 12 weeks[19]. It was found that ambrisentan improves exercise capacity in patients with PAH. In ARIES 3 trial, ambrisentan was given to patients belonging to all groups of pulmonary hypertension[20]. Patients received 5mg ambrisentan once daily for 24 weeks. Primary end point was change in 6 minute walk distance from baseline. There was an increase in 6 minute walk distance of 21m from baseline in the overall population. However , increase in 6MWD was not observed in several non-group 1 PH patients.

An increased incidence of peripheral oedema has been reported , but hepatotoxicity is less for ambrisentan.

Phosphodiesterase 5 inhibitor

Inhibition of type 5 phosphodiesterase leads to increased concentration of cyclic guanosine monophosphate (cGMP) in vascular smooth muscles resulting in vasodilation. The two available drugs in this group for treatment of pulmonary hypertension at present are sildenafil and tadalafil.

Sildenafil: Sildenafil is an oral phosphodiesterase inhibitor. It is a potent pulmonary selective vasodilator. In the SUPER study, 278 patients with PAH (IPAH, connective tissue disease associated or those with congenital systemic to pulmonary shunts) received 20, 40 or 80mg sildenafil orally thrice daily[21]. There was a significant increase in 6 minute walk distance of 45m, 46m and 50m respectively in the three dosage groups at 12 weeks. After one year of treatment there was an improvement of 6MWT distance of 51m in patients receiving sildenafil. FDA has approved sildenafil for patients with PAH in any functional class at a dose of 20mg three times daily.

Sildenafil improves pulmonary hemodynamics in patients with PH secondary to COPD. But it reduces arterial oxygenation due to inhibition of hypoxic pulmonary vasoconstriction. In the study done by Isabel Blanco et al, it was found that at rest sildenafil worsened arterial oxygenation due to greater ventilation-perfusion mismatch[22]. But there was no further worsening of arterial oxygenation with exercise. In a study done on a small number of patients

with interstitial lung disease associated pulmonary hypertension by Corte TJ et al, it was found to improve 6MWT distance[23]. More randomised controlled trials are required to study the efficacy of sildenafil in group 3 pulmonary hypertension.

Tadalafil : Tadalafil is a selective phosphodiesterase 5 inhibtor. It is an oral drug and has the advantage of once daily dosing. Recommended dose is 40mg once daily. In the PHIRST and PHIRST 2 studies , it was shown to improve 6MWT distance.

Combination therapy:

Two or more drugs which acts on different pathways can be used in patients with incomplete response to a single agent. The drugs used for combination therapy are endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostanoids and other novel therapeutic agents. This is similar to systemic hypertension where multiple agents with different mechanisms of action can be used.

BREATHE -2 trial showed a better haemodynamic effect by combining epoprostenol and bosentan[24]. Inhaled ilaprost was combined with bosentan in the STEP-1 study , and it was found to increase the 6MWT distance marginally[25]. Combination therapy is reserved for patients not responding adequately to monotherapy.

New drugs

Riociguat: Riociguat is a novel soluble guanylate cyclase stimulator being investigated for treatment of pulmonary arterial hypertencion, and chronic thromboembolic pulmonary hypertension. It was found to significantly improve exercise capacity in patients with pulmonary arterial hypertension in the PATENT 1 study[27]. In another study, the CHEST-1 oral riociguat significantly improved exercise capacity in patients with chronic thromboembolic pulmonary hypertension.

Imatinib mesylate: It is a tyrosine kinase receptor blocker, and inhibits platelet derived growth factor signalling. It inhibits vascular smooth muscle cell proliferation. In the recently published IMPRES study, imatinib mesylate was found to improve exercise capacity and hemodynamics in patients with advanced PAH[26]. But there were significant serious adverse events requiring discontinuation of the drug. So further studies are required to investigate the long term safety and efficacy of this drug.

Surgical Treatment

Atrial septostomy: Patients with Eisenmenger's syndrome and those with IPAH with patent foramen ovale had a better prognosis compared to those without a patent foramen ovale. This observation supported the idea of atrial septostomy for patients with disabling right heart failure. The creation of an inter atrial right to left shunt can decompress the right cardiac chambers. Recommended technique is graded balloon dilation atrial septostomy. Atrial septostomy should be regarded as a palliative procedure in patients with recurrent syncope or right heart failure in spite of maximal medical therapy.

Lung transplantation: Patients who do not have an adequate clinical response in spite of aggressive medical management should be considered for lung transplantation. Double lung and heart lung transplantation are the preferred procedures. Survival after lung transplantation is 65%, 55% and 44% after 1 year, 3 years and 5 years respectively.

Conclusion

At present pulmonary hypertension is an incurable condition with poor prognosis. As the symptoms and signs are nonspecific, the diagnosis is often delayed. All patients diagnosed with pulmonary hypertension should be evaluated in detail to rule out an underlying cause that can be successfully treated. In the last decade several drugs have been available for targeted treatment of pulmonary hypertension . The new drugs have significantly improved the survival of patients with pulmonary hypertension. Recently increasing data are available regarding the use of combination therapy for treating PH. However more research is required to assess the safety and efficacy of these drugs in long term use.

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