Faridpur Med. Coll. J. 2012;7(2):82-87

ReviewArticle

Pulmonary Hypertension: A Review

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Abstract :

Pulmonary hypertension is a relatively common disorder that leads to right heart failure if untreated. Symptoms and signs of pulmonary hypertensionare often subtle and nonspecific. As a result a significant delay between the onset of symptoms and the diagnosis of pulmonary hypertension is common. Recently improved understanding of the pathophysiology of pulmonary hypertension leads to various treatment options that enable us to treat this disorder more efficiently.

Key words : pulmonary hypertension, primary pulmonary hypertension, pulmonary arterial hypertension.

Introduction :

The lung has a unique double arterial blood supply from the pulmonary and bronchial arteries as well as double venous drainage into pulmonary and azygos veins. The pulmonary circulation is a low pressure, low resistance circuit due to its large cross-sectional area and high capacitance. Pulmonary Hypertension (PH) is defined as a mean pulmonary arterial pressure >25 mm Hg at rest or 30mm Hg with exercise at catheterization. Raised pulmonary arterial pressure causes increased impedance to right ventricular ejection. This increased afterload, if severe or unrelieved, leads to right heart failure.

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Classification of Pulmonary hypertension :

PH has traditionally been divided into two forms: primary and secondary. The etiology of primary pulmonary hypertension (PPH) is unknown. Secondary Pulmonary hypertension results from disorders of respiratory, cardiac and some extra thoracic systems. Recently, a new diagnostic classification was proposed by a World Health Organization (WHO) symposium (table-1)[1]. In this classification, forms of PH are grouped according to shared pathologic processes.

Table I: The WHO diagnostic classification of pulmonary hypertension.

Pulmonary arterial hypertension
Primary Pulmonary hypertension
Sporadic
Familial
Related to:
Collagen vascular disease
Congenital systemic to venous shunts
Portal hypertension
HIV infection
Drugs / Toxins- Anorexigens and others
Persistent pulmonary hypertension of the newborn
Other

Pulmonary venous hypertension
Left sided atrial or ventricular heart disease
Left sided valvular heart disease
Extrinsic compression of central pulmonary veins
Fibrosing mediastinitis
Adenopathy / tumors
Pulmonary venoocclusive disease
Other
Pulmonary hypertension associated with disorders of respiratory system and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep disorder breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Neonatal lung disease
Alveolar capillary dysplaxia
Other
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries.
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
In situ thrombosis
Sickle cell disease
Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
Inflammatory
Schistosomiasis
Sarcoidosis
Other
Pulmonary capillary hemangioma

Clinical features :

Symptoms of PH are often very nonspecific. Significant delay between the onset of symptoms and the diagnosis of PH is common.

Dyspnea on exertion, fatigue and syncope are the most common presenting symptoms. These reflect an inability to increase cardiac output when needed. Chest pain is also very common, due to angina from right ventricular ischemia or related to pulmonary artery stretching. Hemoptysis may occur due to rupture of distended pulmonary vessels. Hoarseness of voice may result from compression of the recurrent laryngeal nerve by the enlarged pulmonary artery. Raynaud's phenomenon occurs in 2% of patients with PPH, but is more common in PH related to connective tissue disease[2].

Signs of PH are mainly localized to the cardiovascular system. Features of PH and right ventricular hypertrophyinclude jugular venous distension, a loud second heart sound in pulmonary area and a tricuspid regurgitation murmur. Hepatomegaly and dependent edema are signs of advanced PH.

Diagnostic assessment :

A high index of suspicion combined with meticulous history and physical examination are essential for the diagnosis of PH. Attention should be given to prior medical conditions, all drugs used, family history and an extensive review of systems.

Electrocardiogram (ECG) : Signs of right ventricular hypertrophy or right atrial enlargement may be present. ECG findings include P-pulmonale, right axis deviation, right bundle branch block and R/S ratio >1 in lead v1. The ECG findings are more in higher pulmonary pressure.

Chest x-ray : The right pulmonary artery diameter >16mm on standard chest x-ray is a valuable sign.

Echocardiography : It is the most useful tool to detect PH and to exclude underlying congenital, valvular or myocardial disease. Echocardiographic findings include right ventricular hypertrophy, right atrial enlargement and tricuspid regurgitation. Pulmonary artery systolic pressure can be obtained from tricuspid regurgitant flow.

Arterial blood gas analysis : Normal resting oxygenation does not exclude exertional or nocturnal oxygen desaturation. About 20% of patients with COPD and normal awake arterial oxygen saturation have nocturnal nonapneic oxygen desaturation. Exertional oxygen desaturation is common.Exercise and sleep oxymetry should be done in all patients.A polysomnogram is indicated if the clinical presentation suggests sleep apnea.

Pulmonary function test : Necessary to establish airflow obstruction or restrictive lung disease. PH can occur when pulmonary function is severely reduced and patient is hypoxic.

High resolution CT scan : Useful to exclude occult interstitial lung disease and mediastinal fibrosis.

Ventilation-perfusion lung scan : Is a reliable method of differentiating chronic thromboembolic PH from PPH. In ventilation-perfusion scan one or more segmental or larger perfusion defect is a sensitive marker of embolic obstruction. In PPH the scan is either normal or may show patchy subsegmental abnormalities.

Pulmonary angiography: If ventilation-perfusion scan is suggestive of chronic thromboembolism, pulmonary angiography can be done to confirm the diagnosisand consider possible surgical thromboendarterectomy.

Cardiac catheterization : Remains the gold standard for the diagnosis and quantification of PH. It is useful in the diagnosis of occult systemic to pulmonary shunts, congenital heart disease and distal pulmonary artery stenosis.

Other investigations : All patients with PH should be extensively evaluated so that a treatable cause can be managed. Initial laboratory evaluation includes complete blood count, prothrombin time, partial thromboplastin time, liver function test and serologic test for collagen vascular disease, if any suspicion. For specific autoimmune disease autoantibodies might include anti-nuclear and anti-DNA (systemic lupus erythematosus), anti-Scl-70 and antinucleolar (scleroderma), anticentromere (CREST syndrome), rheumatoid factor (rheumatoid arthritis), anti-Ro and anti-La (Sjogren's syndrome), anti-Jo-1 (dermatomyositis/polymyositis) and anti U1 RNP (mixed connective tissue disease). HIV testing should also be done in patient with a compatible history or risk factors.

Prognosis :

The prognosis of PPH is highly variable. In one study, median survival of PPH after diagnosis is only 2.8 years[3]. In patients without evidence of right ventricular dysfunction, survival >10 years is possible with new treatment modalities. The 6-minutre walk test is predictive of mortality in patients with PPH and is useful for following a response to therapy.

In secondary PH, the prognosis depends on the underlying disease and right ventricular function. Patient with COPD with PH have a 3-year mortality of 50%, after the onset of right ventricular failure.

Management :

The treatment of PH is complex, potentially dangerous and rapidly evolving. Table 2 lists possible treatment options for patients with PH.

Table II: Treatment options for pulmonary hypertension

Correction of underlying cause Immunosuppressant for autoimmune disease Surgical correction of systemic to pulmonary shunt Discontinue anorectic therapy Antiretroviral therapy if HIV positive Consider liver transplant for portopulmonary hypertension Afterload reduction, digoxin, diuretics and possible revascularization for left ventricular dysfunction
Correction of hypoxemia
Reduction of volume overload Low sodium diet Diuretics
Vasodialtors Calcium channel blockers Bosentan and other endothelin receptor antagonists Epoprostenol or analogs Nitric oxide Sildenafil and other Phophodiesterase (PDE) 5 inhibitors
Anticoagulants
Inotropes Digoxin Parenteral inotropes if decompensated
Surgery Thromboendarterectomy Atrial septostomy Lung transplantation

General measures :

A primary goal in the management of PH is the early identification of any underlying disease while it is still potentially reversible. For example, PH associated with autoimmune disease may respond to corticosteroids or other immunosuppressive therapy. Abolition of systemic to pulmonary shunt at early stage by corrective surgery can restores pulmonary blood flow and pressure to normal. Improvement of PH may be seen following discontinuation of anorexic drugs, although this is uncommon. PH does not necessarily imply total disability for the patient. However, physical activity can be associated with elevated pulmonary artery pressure and marked hemodynamic changes occur early in the onset of increased physical activity.

Graded exercise activities, such as walking, swimming or bike riding are thought to be safer than isometric exercise like stair climbing or lifting weights, which can be associated with syncopal events and should be avoided.

The pathophysiological changes that occur in pregnancy can potentially activate the disease and result in death of the mother and/or the child. Increasedcirculating blood volume and oxygen consumption increases right ventricular work. Circulating procoagulant factors and the risk of pulmonary embolism from deep vein thrombosis and amniotic fluid are of serious concern. Syncope and cardiac arrest have also been reported to occur during active labour and delivery. A syndrome of postpartum circulatory collapse has been described. For these reasons, pregnancy should be strongly discouraged and surgical sterilization should be done in these patients[4].

Medical therapy :

Medical therapies are targeted at reversing the severity of PH via many different pathways. However, these patients often suffer from right heart failure and thus measures that have been shown to be effective in heart failure are often used.

Oral calcium channel blockers :

These agents can reverse pulmonary vasoconstriction and prolong life in 20% of patient with PPH. But, it's not simple to predict who will respond. Pulmonary vasoreactivity can be tested by using prostacycline, adenosine or nitric oxide during right heart catheterization. A minimal acceptable response would be a reduction in mean pulmonary artery pressure of 10 mm Hg associated with either no change or an increase in cardiac output[1]. In patients with acute vasoreactivity, long term therapy with high dose oral calcium channel blockers can produce sustained hemodynamic response and increase survival[5].The reduction in pulmonary artery pressure and pulmonary vascular resistance can be maintained for more than 15 years[6]. Disadvantage of these agents is they can produce profound systemic hypotension. Patient who do not have an acute vasodilator response are unlikely to benefit from calcium channel blockers. Patients who do respond will show marked clinical improvement within first few months.

Epoprostenol (prostacyclin) :

It is one of the most important advances in the treatment of PPH. Epoprostenol is also effective to some extent in pulmonary arterial hypertension due to congenital heart disease, collagen vascular disease and portopulmonary hypertension[7]. It is a potent, short acting vasodilator and inhibitor of platelet aggregation. Continuous intravenous infusion of epoprostenol can improve exercise capacity, quality of life, hemoydnamics and long-term survival[8]. Epoprostenol is administered through a central venous catheter that is surgically implanted and delivered by an ambulatory infusion system. The delivery system for continuous infusion is complex and requires the patients to learn the techniques. Abrupt cessation of long-term therapy is poorly tolerated and potentially catastrophic.

Treprostinil :

Treprostinil is a stable prostacyclin analog that has pharmacological actions similar to Epoprostenol. It's administered subcutaneously through an ambulatory microinfusion pump.Treprostinil can improve significantly 6-minute walk distance and pulmonary haemodynamics in patients with pulmonary arterial hypertension[9]. Although effective it can cause infusion site pain in most patients, thereby limiting its long-term therapy.

Inhaled aerosolized iloprost :

It is also a prostacyclin analog, has been approved for use via inhalation. Inhaled iloprost have an acute effect on pulmonary haemodynamics similar to those of inhaled nitric oxide. Pulmonary vasodilation and improvement in right ventricular function and exercise capacity in patients with PPH have been demonstrated over a 1- year period[10]. This form of therapy is well tolerated but requires frequent (up to 12/day) inhalations. Side effects such as coughing are usually minor and transient.

Beraprost :

It is a prostacyclin analog that is suitable for oral administration. Improvements in exercise capacity and pulmonary haemodynamics in patients with PPH and chronic thromboembolic PH, has been shown in small, prospective uncontrolled studies[11]. Beraprost improve exercise capacity and symptoms over a 12-week period, but there is loss of effectiveness over 1 year[12].

Bosentan :

Bosentan is an endothelin-1 receptorantagonist for the treatment of PPH, approved by the Food and Drug Administration. Endothelin-1has a very potent vasoconstrictor, proliferative and profibrotic effect. High concentrations of endothelin-1were noted in plasma and lung tissue of patients with PH. Although it

remains unclear whether endothelin-1causes PHor is simply a mediator, results of clinical trials are encouraging[13]. It has been established in several multi centre trials that bosentan can significantly improve 6-minute walking distance and pulmonary hemodynamics[14]. Only disadvantage of bosentan therapy is that it can cause serious liver injury, so serum aminotransferase levels must be measured prior to initiating bosentan therapy and monthly thereafter.

Nitric oxide :

Nitric oxide is an endogenous vasodilator, approved for persistent PH of newborn. In adults its use is limited in acute vasoreactivity testing and short term therapy in critically ill patients. Inhaled nitric oxide decreases pulmonary vascular resistance without affecting systemic vascular resistance[15]. Although inhaled nitric oxide is highly effective in PH, but its cost and technical difficulties in delivery have limited its use.

Sildenafil :

Sildenafil is a potent inhibitor of phosphodiesteraase-5 which is abundant in vascular, tracheal and visceral smooth muscle in addition to corpora cavernosa. Initially it was approved to treat erectile dysfunction and recently for pulmonary arterial hypertension. It can cause a preferential pulmonary vasodilatation, which makes it the drug of choice for long term treatment of PH, both primary and secondary. In a small trial, 16 patients with PH secondary to pulmonary fibrosis received nitric oxide inhalation and were then randomized to treatment with oral sildenafil or intravenous Epoprostenol. Only those patients who received sildenafil had a reduction in the ratio of pulmonary to systemic vascular resistance. Both nitric oxide and sildenafil raised arterial partial pressure of oxygen[16]. Sildenafil produce pulmonary vasodilatation by promoting an enhanced and sustained level of cGMP, an identical effect to that of inhaled nitric oxide. The recommended dose is 20mg three times daily, but dosages as high as 80 mg three times daily have been used safely.

Warfarin :

Chronic anticoagulation is recommended to prevent thrombosis and can prolong life in PPH[17]. A retrospective review of patients with PPH monitored over a 15-year period at the Mayo clinic has suggested that patients who received warfarin had improved survival over those who did not. Warfarin is also found to be beneficial in patients who failed to respond to high dose oral calcium channel blockers. Patients are prone to thromboembolism because of sluggish pulmonary blood flow, dilated right heart chambers, venous insufficiency, and relative physical inactivity. The current recommendation is to use warfarin in relatively low doses with the international normalized ratio maintained at approximately 2.0.

Digoxin :

Digoxin can exert a favourable haemodynamic effect when given acutely to patients with right heart failure due to PPH. An increase in resting cardiac output of about 10% was noted. But its long term consequences are controversial. The short term use of parenteral inotropes and digoxin may be of benefit in patients with decompensated right heart failure[18].

Diuretics :

Judicious use of diuretic is needed in some patients with PPH having right ventricular failure and systemic venous congestion. Patients with advanced PPH can have increased left ventricular filling pressures that contribute to the symptoms of dyspnoea and orthopnoea, which can be relieved with diuretics. Diuretics can also reduce right ventricular wall stress in patients with tricuspid regurgitation and volume overload.

Supplemental oxygen :

In patients with alveolar hypoxia from parenchymal lung disease hypoxic pulmonary vasoconstriction can contribute to PH. Supplemental low flow oxygen alleviates arterial hypoxemia and attenuates the PH. Patients with severe right heart failure and resting hypoxemia should be treated with continuous oxygen therapy to maintain their arterial oxygen saturation above 90%[4].

Surgical therapy :

Patients with chronic thromboembolism, PH may be considered for surgical thromboendarterectomy. As the procedure is of considerable risk, surgery should be done only if the disease is very severe. Survivors usually change from functional status of NYHA class III or IV to NYHA class I or II.

Balloon atrial septostomy : It creates a right to left interatrial shunt in order to unload the right ventricle and increase systemic cardiac output in PPH. Indications for the procedure include recurrent syncope and/or right ventricular failure, despite maximal medical therapy, as a bridge to transplantation if deterioration occurs despite maximum medical therapy.

The disease process appears to be unaffected by the procedure, so the effects are only palliative and short lasting. Unfortunately, procedure-related mortality is significant and the procedure is considered investigational[19].

Lung transplantation : It is an option for patients <65 years old with PH not responding to medical managements. The major problem in lung transplantation is the shortage of donor organ. The 5-year survival rate for lung transplantation is about 44%[20]. There is immediate reduction in pulmonary arterial pressure and pulmonary vascular resistance with an improvement in right ventricular function. Recurrence of PPH after transplantation has not been reported.

Pulmonary arterial hypertension associated with congenital heart disease (Eisenmenger syndrome)

PH can develop in adults with an untreated atrial or ventricular septal defect or in patent ductus arteriosus. When pulmonary vascular resistance has increased so that the patient shunts right to left, surgical closure of the anomalous communication is dangerous, and usually fails to relieve PH. Surgery may hasten death in survivors who had either balanced shunts or predominant right to left shunts. Intravenous Epoprostenol has been shown to improve exercise tolerance, quality of life and haemodynamics in these patients with Eisenmenger syndrome. In patient with bidirectional shunts, the use of Epoprostenol may be a therapeutic strategy to enable a patient who is considered inoperable to become eligible for surgery at a later date[4].

Conclusion :

Introduction of various vasodilators, phophodiesterase-5 inhibitor and endothelin receptor antagonist have revolutionized the treatment of PH. PH which was once considered a dreadful disease, now can be managed with confidence. But the treatment option for this disorder is still very complex and costly, more so in developing countries like ours. Sildenafil offers hope for patients in developing countries as it is cheaper and easy to administer. More clinical trials are needed to evaluate its role in PH, especially in secondary PH due to congenital heart disease, which is very common in our country.

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