Page No. 13-16

PULMONARY PERSPECTIVE PAH

Dr. Manish Kumar [1], Prof D P Singh[2]

Received:- 18/08/2023
Revised:- 29/08/2023
Accepted:- 30/08/2023

Address for Correspondence:
1. MD (Med), DTM&H (UK), FICP, FIACM, FIAMS
Fellow Royal Soc of Trop Med (UK)
Consultant Physician, Arc Hospital, Bhahalpur- 812001

2.MD DTCD, FICP, FRCP, FICS, FCSI, FCCP
FACP, FIAMS Ex-Professor & Head of Department of
Respiratory Medicine Jawahar Lal Nehru
Medical College, Bhagalpur Chairman STF
RNTCP Bihar, Member Governing Body API

ABSTRACT

Pulmonary hypertension associated with lung diseases is the second most common form of PH. The most common respiratory causes of Pulmonary hypertension are chronic obstructive pulmonary disease (COPD), Interstitial Lung Disease (ILD) and Obstructive sleep apnea (OSA). PH may also occur due to high altitude exposure and in patients with cystic fibrosis. PH in patients with obstructive of restrictive lung disease has poor outcomes.[1] Patients with Interstitial Lung Diseases (ILD) may develop Pulmonary Hypertension during the course of disease. This can occur in the absence of advanced pulmonary dysfunction or significant hypoxaemia, hence it may not be well recognized. ILD's most commonly associated with Pulmonary hypertension include connective tissue disease related ILD, Sarcoidosis, Idiopathic pulmonary fibrosis, and pulmonary Langerhans cell histocytosis. The patients with ILD may develop PH due to various mechanisms like pulmonary vasoconstriction and remodelling, progressive parenchymal fibrosis, perivascular fibrosis, vascular inflammation and thrombotic angiopathy. A high index of suspicion is needed for diagnosis as the clinical presentation is often nonspecific. Colour Doppler echocardiography is the most important non-invasive clinical tool that helps in assessment of degree of PH along with the cardiac status. Right heart catheterization is also helpful in confirmation of PH, along with assessing its severity and planning for further management. Management of PH in patients with lung diseases depends on the underlying cause. An increasing number of pharmacological agents are now available for the possible treatment in patients with PH.

INTRODUCTION

Pulmonary hypertension associated with lung diseases and hypoxia is associated with increased morbidity and mortality. It has been classified as Group 3 in 2008 Dana Point classification of PH.[2] The prevalence of PH in COPD depends on the classification. According to the latest criteria from the World symposium using mPAP>20 mmHg, upto 90% of patients with stage IV COPD have mPAP >20mmHg and upto 5% of patients have severe PAH with mean PAP >35-40mmHg.[3,4] Interstitial lung diseases (ILD's) comprise a heterogenous group of diseases with common functional characteristics of impaired gas exchange and restrictive physiology eventually leading to irreversible fibrosis. In patients with ILD 8-15% are diagnosed with mPAP >25mmHG and upto 60% with end stage disease. ILD associated with PH has adverse outcomes with frequent exacerbations as compared to idiopathic PAH (IPAH).[5,6]

The dyspnea and exercise limitation in patients with ILD is often due to Pulmonary hypertension. Connective tissue disease (CTD) related ILD, sarcoidosis, idiopathic pulmonary fibrosis (IPF) and pulmonary Langerhans cell histocytosis (PLCH) are ILD's most commonly associated with PH.

PATHOLOGY OF GROUP 3 PH

In hypoxic lung disease, there are multifactorial causes leading to PH. In patients with chronic lung disease, there is a loss of blood vessels resulting in a reduced capacity to accommodate higher cardiac output leading to an increase in pressure. Most chronic and severe lung diseases result in periods of continuous or intermittent hypoxia. Alveolar hypoxia results in contraction of pulmonary vessels. In the early stages it may be reversible with increase in inspired oxygen concentration. However, chronic hypoxia results in release of vasoconstrictors such as endothelin and serotonin with cause intimal hyperplasia. This remodelling is only partially reversed with oxygen. Studies have shown an inverse relationship between PAP and Pao2.[7]

PREVALENCE OF PH IN ILD

The overall prevalence of PH in ILD is not fully known and varies according to the diagnosis and severity of lung impairment. A study done by Leuchte et.al[8] among 88 ILD patients undergoing right heart catheterization reported the incidence to be 31.8%. The prevalence and characteristics of PH associated with specific ILD's are summarized in Table 1.

Table 1. :- Prevalence and Potential Mechanism of PH in specific ILD's.[9-13]

Disease	Prevalence of PH	Potential Mechanism
Pulmonary Langerhans Cell Histocytosis (PLCH)	Upto 100% in advanced disease	Intrinsic proliferative pulmonary vasculopathy, parenchymal fibrosis, hypoxic vasoconstriction
Connective tissue disease related ILD	Upto 45% in Scleroderma ILD	Vasoconstriction & remodelling, insitu thrombosis & thromboembolisem
Sarcoidosis	Upto 74% in advanced disease	Vascular obstruction/ destruction associated with parenchymal fibrosis, granulomatous vasculopathy

Access this article online

Website:
www.onlinepjm.com

Quick Response Code

How to cite this article:

Kumar M, Prof D P Singh, Pulmonary Perspective Pah

Idiopathic Pulmonary Fibrosis	Upto 84%	Vascular obstruction/ destruction associated with parenchymal fibrosis, hypoxic vasoconstriction
Pneumoconiosis	Unknown	Vascular obstruction/ destruction associated with parenchymal fibrosis, hypoxic vasoconstriction & remodelling

SARCOIDOSIS

In patients with sarcoidosis, PH is a predictor of mortality. The compression by enlarged lymph nodes leading to pulmonary artery stenosis and direct granulomatous involvement of the arterial walls are also additional causative factors. The prevalence of PH was found to be 73.8% after right heart catheterization in Sarcoidosis patients listed for lung transplantation at United Network for Organ Sharing. In a cross-sectional study among Sarcoidosis patients, the prevalence was found to be 5.7% based on Echocardiography.[14]

SYSTEMIC SCLEROSIS

A study by Trad et.al found a combination of PH in ILD patients to be 21%. PH was found to be a risk factor for survival but there was no close correlation between PH and the severity of restrictive ventilator defect.[15]

IDIOPATHIC PULMONARY FIBROSIS

IPF is a progressive fibrotic disorder of the lung of unknown cause associated with high mortality. It is characterized by histopathological pattern of usual interstitial pneumonia. Studies have demonstrated that IPF patients with PH have significant exercise limitation as compared to patients without PH but with equally severe restrictive lung physiology. The prevalence of PH in IPF patients was found to be upto 84%.[16]

PULMONARY LANGERHANS CELL HISTOCYTOSIS (PLCH)

PH is common in patients with end stage PLCH and tends to be more severe as compared to other advanced lung diseases such as emphysema. There is a lack of correlation between mean PA Pressure as assessed by echocardiography or cardiac catheterization and the degree of respiratory symptoms. PH is not limited to end stage PLCH.[17]

PNEUMOCONIOSIS

They are caused by inhaled dust such as asbestos and silica that cause varying degrees of fibrotic reaction in the lungs. A hemodynamic study of subjects with asbestosis revealed that a higher mean PA Pressure was seen with increasing severity of parenchymal opacities.[18]

DIAGNOSIS & STAGING

Exertional dyspnea and exercise limitation is the most common symptom associated with both ILD and PH. Hence development of PH in a patient with ILD may be difficult to recognize at an early stage. Patients with advanced PH may present with physical signs such as loud pulmonic component and fixed splitting of second heart sound, diastolic murmur of pulmonary regurgitation and holosystolic murmur of tricuspid regurgitation. Early diagnosis of PH in patients with ILD before the physical signs become evident is a clinical challenge that requires a high index of clinical suspicion. Studies have shown that patients with ILD should be screened for PH as even mild PH may have adverse prognosis on the clinical outcome of patients with ILD.

RADIOLOGY

The sensitivity of chest radiograph is generally low. Chest X Ray may show signs such as enlarged central pulmonary arteries (>15 mm). Patients with moderate to severe PH may present with enlarged main pulmonary artery (>29mm) or an increased diameter of the pulmonary artery as compared to aorta on CT scan.

ECHOCARDIOGRAPHY

Transthoracic colour Doppler echocardiography (TTE) is the most appropriate non-invasive method for detecting PH. Doppler echocardiography can estimate the level of systolic PAP and assess the presence of associated abnormalities such as right atrial or right ventricular enlargement, right or left ventricular dysfunction, intracardiac shunt, valvular disease and pericardial effusion. Estimation of right ventricular systolic pressure by tricuspid regurgitation jet velocity using the Bernoulli's equation has been reported to be useful in up to 86% of cases.[19] The measurement may be difficult in patients with obstructive pulmonary diseases with poor echo window. Changes in PAP with exertion may be measured using supine bicycle exercise with echocardiography.

RIGHT HEART CATHETERIZATION

Right heart catheterization is the gold standard for evaluating PH and measuring pulmonary hemodynamic parameters. It is useful for confirmation of PH, its severity, assessment of prognosis and guidance regarding therapy. A short acting agent such as intravenous epoprostenol, adenosine or inhaled nitric oxide is used for vasoreactivity testing. A positive vasodilator response is generally defined as a decrease in mean PAP of at least 10 to 40 mmHg or lower with an increased or unchanged cardiac output. A positive vasodilator test in idiopathic PAH usually indicates that the patient is responsive to high dose calcium channel blocker (CCB) therapy. However, vasoreactivity testing and high dose CCB therapy has no role in management of PH in association with IPF and other ILD's.[20]

PULMONARY FUNCTION TEST

Generally, the assessment of PH does not depend upon (Pulmonary Function Tests) PFT. However, the patients of emphysema with IPF may present with nearly normal lung volumes

associated with a severely reduced diffusing lung capacity as measured by carbon monoxide transfer factor via single breath method (DLCO). This discrepancy is associated with a higher probability of PH.[17,18] Studies have suggested that in patients with IPF and in Sarcoidosis, the need for oxygen supplementation and DLCO <40% are predictive of PH.[21]

PULMONARY FUNCTION TEST

Generally, the assessment of PH does not depend upon (Pulmonary Function Tests) PFT. However, the patients of emphysema with IPF may present with nearly normal lung volumes associated with a severely reduced diffusing lung capacity as measured by carbon monoxide transfer factor via single breath method (DLCO). This discrepancy is associated with a higher probability of PH.[17,18] Studies have suggested that in patients with IPF and in Sarcoidosis, the need for oxygen supplementation and DLCO <40% are predictive of PH.[21]

HISTOLOGY

Histology is not needed to confirm a diagnosis of PH. In patients with PH (PA Pressure > 30mmHg), transbronchial biopsy obtained via bronchoscopy is relatively contraindicated due to increased risk of bleeding. Surgical lung biopsy also carries an increased risk of morbidity and mortality.

GENERAL DIAGNOSTIC APPROACH

The clinician should be mindful of the fact that PH could be due to other causes as well in patients with ILD. For example, pulmonary embolism or CTD. Therefore, other noninvasive investigations like Transthoracic Colour Doppler Echocardiography, PFT, estimation of BNP or NT-pro-BNP, overnight oximetry and CT chest angiography should be done as appropriate. If the results are suggestive of PH, RHC including vasoreactivity testing should be performed.

MANAGEMENT OF GROUP 3 PH

The management of PH depends on the underlying cause. In patients with COPD, drugs like sildenafil and bosentan have been found to be useful in improving the pulmonary hemodynamics. However, it is of limited usefulness in improving the exercise capacity and quality of life. Studies have shown that the levels of NTproBNP in severe group 3 PH is reduced with pulmonary vasodilators, however there is no significant increase in 6 min walk distance.

An accurate diagnosis of underlying ILD is imperative to establish a correct approach to treatment. This may require surgical lung biopsy for histological differentiation. Treatment of most ILDs consist of immunosuppressive or anti-inflammatory regimens with prednisone eventually combined with a cytotoxic agent such as azaithioprine or cyclophosphamide.[22,23] The preservation of lung function in IPF may be enhanced if a high dose N-acetylcysteine therapy is added to prednisone and aziathioprine. It appears to exert antioxidative effects by replenishment of glutathione stores.[24]

General treatment guidelines recommend administration of diuretics in patients with volume overload due to right heart failure along with use of digitalis if required. Oxygen status should be assessed at rest and during exercise. Long term oxygen therapy should be initiated to maintain Spo_2 >90%. Anticoagulation is also beneficial in avoiding pulmonary embolism and insitu thrombosis in these patients.

VASOMODULATING THERAPY

The aim of therapy for PH is relief of pulmonary vasoconstriction and reversal or reduction of cellular proliferation and vascular remodelling. A number of drugs including nonselective endothelin A/B receptor antagonist bosentan; prostacyclin analogues epoprostenol, treprostinil and iloprost and phospodiesterase 5 inhibitor sildenafil are available for treating PH. [24] The treatment of ILD with PH using systemic vasodilator therapy may be complicated by worsening hypoxaemia due to increased ventilation-perfusion mismatch. The patient's response to therapy can be assessed by dyspnea, exercise capacity, quality of life and hemodynamic parameters measured by serial echocardiography or right heart catheterization.

LUNG TRANSPLANTATION

The patients with progressive or severe impairment due to PH or ILD may be considered for lung transplantation. The International Society of Heart and lung transplantation report suggests that long term outcome is better with double lung transplantation. [25] In older patients with pulmonary fibrosis and mild to moderate PH, single lung transplantation is appropriate.[25]

PROGNOSIS

Pulmonary hypertension causes premature death and disability in patients with or without underlying lung disease. In patients with both ILD and PH, the prognosis is affected by both PH and underlying ILD. The presence of PH in patients with ILD suggests a poor prognosis. Studies have shown that patients with PAP more than 50mmHg had a median survival of less than 1 year.[26]

CONCLUSION

Pulmonary hypertension is an under recognized complication in patients with pulmonary diseases. It may arise through various mechanisms. The presence of PH in these patients results in an increase in symptoms, functional impairment, morbidity and mortality. More studies are needed to understand the changes leading to PH in patients with lung diseases. This may lead to identification of therapeutic targets that will improve outcomes.

REFERENCES

1. McGettrick M, Peacock A. Group 3 pulmonary hypertension: Challenges and opportunities. Glob Cardiol Sci Pract. 2020 Apr 30;2020(1):e202006. doi: 10.21542/gcsp.2020.6. PMID: 33150151; PMCID: PMC7590933.

2. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl.):S43-54.
3. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1).
4. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53(1).
5. Kimura M, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishiyama O, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration.2013;85(6):45663.
6. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J. 2015;46(5):13707.
7. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008;32(5):137185.
8. Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir CritCare Med.* 2006;173:744-750.
9. Vassallo R, Ryu JH. Pulmonary Langerhans' cell histiocytosis. *Clin Chest Med.* 2004;25:561-571.
10. Sundar KM, Gosselin MV, Chung HL, Cahill BC. Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. *Chest.* 2003;123:1673-1683.
11. Hoeper MM. Pulmonary hypertension in collagen vascular disease. *Eur Respir J.* 2002;19:571-576.
12. Fagan KA, Badesch DB. Pulmonary hypertension associated with connective tissue disease. *Prog Cardiovasc Dis.* 2002;45:225-234.
13. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. Chest 2006; 129: 1246–1252.
14. Shorr A, Davies D, Nathan S. Outcomes for patients with sarcoidosis awaiting lung transplantation. Chest 2002; 122: 233–238.
15. Trad S, Amoura Z, Beiglman C, et al. Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease. Arthritis Rheum 2006; 54: 184–191.
16. Shorr Af, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplantation. Eur Respir J 2007; 30: 715–721.
17. Sundar KM, Gosselin MV, Chung HL, Cahill BC. Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. *Chest.* 18. Tomasini M, Chiappino G. Hemodynamics of pulmonary circulation in asbestosis: study of 16 cases. *Am J Ind Med.* 1981;2:167-174
19. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167:735-740.
20. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest 2007; 132: 998–1006.
21. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646–664.
22. Brown K, Raghu G. Medical treatment for pulmonary fibrosis: current trends, concepts, and prospects. Clin Chest Med 2004; 25: 759–772.
23. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005; 353: 2229–2242.
24. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126(suppl):35S-6
25. Meyer D, Edwards L, Torres F, Jessen M, Novick R.Impact of recipient age and procedure type on survival after lung transplantation for pulmonary fibrosis. Ann Thorac Surg 2005; 79: 950–957.2S.
26. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest. 2005;128:2393-2399.

***