Review Article

Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Pulmonary hypertension (PH) is likely to complicate chronic obstructive pulmonary disease (COPD) in a large proportion of patients, especially those with severe disease. Majority of patients have a mild to moderate elevation in the pulmonary artery pressure that usually does not require specific treatment. A small subset of patients, however, develops severe PH that is "out-of-proportion" to the severity of COPD. Generally considered a consequence of chronic hypoxaemia, endothelial dysfunction has now been recognised to play an important role in the pathogenesis of PH in COPD. Pulmonary vessels remodelling characterised by intimal enlargement with proliferating smooth muscle cells, medial hypertrophy, arteriolar muscularisation and endothelial cell proliferation, especially affecting the small arterioles and arteries, leads to permanent changes in the vascular structure and function. Clinical recognition of PH is difficult. Echocardiography is used for screening while right heart catheterisation is the gold standard for diagnosis. In patients who have a moderate degree of chronic hypoxaemia, long term oxygen therapy is indicated and is the only therapeutic measure so far known to retard the progress of PH. Newer therapies targeting the specific abnormalities of vasoconstrictor-vasodilator balance, arising as a consequence of endothelial dysfunction, are under investigation and may offer a management option especially in severe PH associated with COPD. **[Indian J Chest Dis Allied Sci 2010;52:29-40]**

Key words: Chronic obstructive pulmonary disease, Smoking, Endothelial dysfunction.

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality in adults all over the world. While other major causes of non-cancer mortality such as coronary artery disease and stroke have shown a consistent downward trend, COPD is the only one that continues to increase.[1] In the United States, in the year 2000, COPD was a major cause for health care utilisation with 8 million physician office / hospital outpatient visits, 1.5 million emergency department visits, and 673,000 hospitalisations.[2] The epidemiological scenario is expected to worsen and the World Health Organization predicts that COPD will become the third leading cause of death (currently fourth) and the fifth leading cause of disability (currently twelfth) worldwide by the year 2020.[3,4]

While the characteristic abnormality in COPD is an inflammatory state of the airways that occurs in response to exposure to noxious stimuli and results in airflow limitation that is only partially reversible, and is usually progressive, the pulmonary involvement extends beyond the airways. A major contributor to airflow limitation is emphysema, the dilation and destruction of airspaces distal to the terminal bronchiole in the lung parenchyma without accompanying inflammation. In recent years, pulmonary vascular pathology is increasingly being recognised as the third important lung involvement that contributes to the morbidity and mortality. The consequence of the pulmonary vascular involvement is an increase in the pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) presenting an increased afterload to the right ventricle. The natural history of COPD usually being one of a progressive downhill course, PH has generally been viewed as a late stage development occurring in patients with severe airways obstruction and a chronic hypoxaemic state. Clinical recognition of early stages of PH is difficult. With limited therapeutic options available to manage PH, it has not received its due attention as a distinct entity within the manifestation complex of COPD. Recent advances in the understanding of PH of idiopathic origin, extension of that knowledge as well as increased understanding of the pulmonary vascular pathology in PH associated with COPD as well as the recognition that it is an important determinant of exercise limitation, dyspnoea and survival have led to renewed interest into the

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pathogenesis and therapeutics of this facet of COPD. Further, identification of a subset of patients of COPD who have an unusually severe form of PH as well as the observation that pulmonary vascular changes may occur in smokers even without hypoxaemia have provided additional impetus into research in PH associated with COPD.

Definition

Pulmonary hypertension is an elevation at rest in the mean PAP above 25mmHg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure of less than 15mmHg and PVR greater than 3 Wood units. In many of the older studies, the cut-off PAP was 20mmHg. In the more recent literature, the cut-off of 25mmHg has been used[5] to bring in a more uniform approach in defining different types of PH, including idiopathic. This figure applies to pressures measured on right heart catheterisation (RHC) in a recumbent position. Cor-pulmonale is the consequence of PH caused by respiratory disorders and is defined as right ventricular hypertrophy and dilatation or both.[6]

Classification

Pulmonary hypertension was earlier classified into primary and secondary forms, the latter being a consequence of a known underlying disease and the former being of unknown origin.[7] A more comprehensive classification was proposed by the World Health Organization in 1998 during the Second World Symposium on Pulmonary Hypertension held in Evian, France.[5] The aim of the Evian classification was to individualise different categories sharing similarities in pathophysiological mechanisms, clinical presentation, and therapeutic options.

The Evian classification[8] consisted of five categories in which PH diseases were grouped according to specific therapeutic interventions directed at dealing with the cause of: *(i)* pulmonary artery hypertension (PAH), *(ii)* pulmonary venous hypertension, *(iii)* PH associated with disorders of the respiratory system or hypoxaemia, *(iv)* PH caused by thrombotic or embolic diseases, and *(v)* PH caused by diseases affecting the pulmonary vasculature. Within each category are subsets that reflect diverse causes and sites of injury. The Evian classification is now well accepted and widely used in clinical practice.

A minor revision was carried out in 2003, during the Third World Symposium on Pulmonary Arterial Hypertension held in Venice, Italy. The most recent revision was carried out in the Fourth Symposium with further refinement and elaboration of categories.[9] Pulmonary hypertension complicating COPD is perhaps the commonest type a pulmonologist encounters. It is placed among the third category, Group III, of the revised WHO classification of PH along with other respiratory conditions that cause chronic hypoxaemia.

PREVALENCE

There is a paucity of worldwide data on prevalence and incidence of PH in COPD. There are also wide variations in the reported prevalence rates in the few studies that have been carried out. This is largely due to the definition of PH and the method of measurement of PAPs. Further, patient selection would also influence the prevalence. Factors including the severity of COPD measured by the degree of airways obstruction, presence of chronic respiratory failure and frequency of acute exacerbations are important. Other likely factors that could potentially influence the occurrence of PH in COPD would include adequacy of treatment including use of oxygen, genetic and perhaps racial factors. Further, presence of comorbidities such as left heart systolic or diastolic dysfunction, sleep apneas and chronic thromboembolism that themselves can cause PH would confound the observed prevalence if such patients are not carefully excluded.

Weitzenblum *et al*[10] observed a prevalence of PH (defined as mean pulmonary artery pressure [MPAP] > 20mmHg) of 35% among patients with severe COPD. Oswald-Mammosser *et al*[11] found a prevalence of resting pulmonary hypertension of only 20.5% in patients with emphysema. However, on exercise, nearly two-thirds of the patients exceeded the PAP cut-off of 30mmHg.

In contrast, in 120 patients with severe emphysema evaluated for participation in the National Emphysema Treatment Trial, end-expiratory pulmonary artery mean pressure was >20mmHg in more than 90% of patients[12]. However, almost 95% of the patients had MPAP of less than 35mmHg. These patients had more severe airways obstruction than those among the earlier study. This study suggested that PAP was likely to worsen with increasing airways obstruction. As COPD is usually a progressive disease, it may be expected that with increasing duration of disease, the prevalence of pulmonary hypertension would increase. Yet the increases are modest in most patients.

Occurrence of severe PH in COPD is distinctly uncommon. Only 27 out of 998 COPD patients had PAP above 40mmHg (severe) on RHC in a study from France.[13] Most of these patients had significant physiological derangements including mild to moderate airway obstruction, severe hypoxaemia, hypocapnia, and very low diffusion capacity. That severe PH is uncommon in COPD was also shown in another study by Thabut *et al*[14] in 115 patients with COPD evaluated for lung volume reduction surgery (LVRS) and lung transplantation. While nearly 50% patients had a mean PAP above 25mmHg, only 3.7% had a severe increase in PAP (>45mmHg).

On a 7-year follow-up with serial RHC, Kessler *et al*[15] demonstrated that the evolution of pulmonary hypertension in patients with moderate degree of airways obstruction was slow. Only 25% of patients developed PH on follow-up that was mild by haemodynamic criteria. Patients who exhibited normal resting but elevated PAP with exercise were more likely to exhibit resting PAP elevation upon follow-up.

The above studies suggest that PH is common in COPD but generally mild to moderate. This contrast with some of the other forms of PH, notably the idiopathic PAH and that due to chronic thromboembolic disease in whom PAP exceeding 40mm is common. However, a small subset of patients with COPD develop severe PH that is "out-of-proportion". This phenotype is the subject of much interest and debate especially with respect to pathogenesis and management.

PATHOLOGY AND PATHOPHYSIOLOGY

Traditionally, PH has been viewed as a late complication in the natural history of COPD, a consequence of chronic hypoxaemia. However, pulmonary vascular changes have been documented in patients with mild COPD that may modify the mechanisms that regulate the pulmonary vascular tone and contribute to maintaining an adequate ventilation-perfusion (VA / Q) matching. The increase in PVR is not only a consequence of a hypoxic vasoconstriction but is largely due to permanent changes in the vascular structure and function. This is called pulmonary vascular remodelling. Pulmonary vascular remodelling is believed to be a result of inflammatory changes induced by products of tobacco smoke but may also be induced or amplified by chronic hypoxaemia and may have a genetic basis to explain different susceptibilities towards developing PH among patients with COPD. A critical component of the pathological changes is the endothelial dysfunction producing an imbalance between vasoactive constrictor and dilator substances.

In patients with mild COPD undergoing resective lung surgery, Barbera *et al*[16] observed narrower lumens and thicker walls produced mainly by an enlargement of the intimal layer that took place predominantly in arteries with small diameters (<500μ) correlating with the degree of ventilation / perfusion mismatching. Morphometrical analysis of pulmonary artery (PA) revealed thicker intimas, especially in small arteries, in both smokers and COPD compared with nonsmokers.[17] This suggested that tobacco smoke plays an important role in the causation of pulmonary vascular pathology in COPD. VA / Q imbalance, predominantly perfusion heterogeneity, was observed to be disproportionately greater than airflow limitation in GOLD stage I suggesting that pulmonary vasculature involvement occurred early during the course of the disease.[18]

Histological lung biopsies reveal vascular remodelling *i.e.* smooth muscle cells proliferation with medial hypertrophy, arteriolar muscularisation and endothelial cell proliferation. This affects small and precapillary arterioles (<80μ). By reducing the lumen, the vascular resistance is increased. While intimal enlargement with proliferating smooth muscle cells is the most prominent change, alterations in the muscular layer are less striking.[16-17,19]

In transverse section, pulmonary arterioles in severe COPD patients have a distinct media of circularly oriented smooth muscle bounded on its outer and inner aspects by elastic laminae. The muscularisation of pulmonary arterioles can extend to the periphery in precapillary vessels as little as 20μ in diameter. This phenomenon is due to hypertrophy, proliferation and transformation of the phenotype of contractile cells called pericytes, which are precursors of smooth muscle cell, or transformation of intermediate cells.[20] However, lesions such as plexiform lesions (irregular mass of endothelial cells) or angiomatoid lesions, characteristic of severe idiopathic PH have not been observed in PH associated with COPD.[21]

Role of Hypoxaemia and Hyperinflation

Vasoconstriction in response to hypoxia is a mechanism to preserve the VA / Q balance in the lungs by diverting blood to better ventilated areas. However, chronic hypoxia has been long been shown to be associated with PH.

It has been proposed that the mechanism of hypoxic pulmonary vasoconstriction involves inhibition of potassium current and pulmonary vascular smooth muscle membrane depolarisation, as a result of changes in the membrane sulfhydryl redox status, related in turn to reduced generation of oxygen radicals during hypoxia.[22] Prolonged hypoxia inhibits expression of voltage-gated potassium channels and reduces channel currents in PA smooth muscle cells. The consequent membrane depolarisation raises cytosolic calcium thus stimulating smooth muscle cell proliferation.[23] Thus, hypoxaemia not only promotes vasoconstriction but also contributes to the process of vascular remodelling. Polycythemia consequent upon the development of chronic hypoxaemia contributes to PH by increasing viscosity of blood.

It is interesting to note that patients who have out-of-proportion PH have only a moderate degree of airways obstruction but marked hypoxaemia without much hypercapnia. These patients may have a more pronounced pulmonary vascular disease.[24] The reason for such a response is not known. Hypoxic pulmonary vasoconstriction is driven by the intrinsic response to hypoxia of two different cell types, namely the pulmonary arterial smooth muscle and endothelial cells.[25] Whether there is an increased reactivity of these cells to hypoxia is not known.

Apart from chronic hypoxaemia, other mechanisms are involved in the pathogenesis of PH in COPD. Destruction of pulmonary capillary bed in emphysema reduced the total cross-sectional area of the pulmonary circulation thus increasing the PVR. As the pulmonary vascular remodelling is widespread, the high capacitance that is the characteristic of pulmonary circulation is impaired because these vessels are narrower, thicker and less compliant. These cannot accommodate increased flow from the emphysematous areas further adding to the increased PVR. With increasing hyperinflation, the tendency for intrinsic positive end-expiratory pressure increases and a positive pressure of 5 to 7.5 cmH_2O can develop in the alveoli physically compressing the capillary bed. These mechanisms that operate especially when emphysema is dominant also explain why the occurrence of hypoxaemia is not inevitable in the pathogenesis of PH in COPD.

Transient and temporary reductions in PaO_2 can also increase PAP that is reversible. However, whether such reductions occurring frequently can lead to persistent elevations of PAP is not established. Majority of patients who have a normal resting PH develop an increase in PAP on exercise[11] as the normal response of decreased PVR to accommodate increased pulmonary flow is impaired. This also suggests that vascular remodelling occurs early in COPD.

In advanced COPD, patients with resting PH have a marked increase in PAP during steady-state exercise. A COPD patient whose baseline PAP is modestly elevated (25-30mmHg) may exhibit severe PH (50-60mmHg) during moderate exercise (30-40W). From a practical viewpoint, this means that daily activities, such as climbing stairs, or even walking, can induce marked PH.[20] During acute exacerbations of COPD, the PAP may increase sufficiently to precipitate right heart failure.[26] PAP may increase by as much as 20mmHg and returns to its baseline value after the recovery of the exacerbation.[27]

It is known that acute exacerbations in COPD hasten the worsening of lung function and that patients with severe COPD including those with PH and chronic hypoxaemia have more frequent exacerbations. The exact link between exacerbations and the natural history of permanent PH in COPD is not precisely known. It can be speculated that the repetition of exacerbations associated with transient increase in PAP could lead to permanent PH.[20]

During sleep, hypoxaemic episodes usually occur during the rapid-eye-movement stage in patients with COPD. It was suggested that these hypoxaemic episodes result from a combination of hypoventilation and impaired VA/Q relationships and that these episodes may contribute to the development of the pulmonary hypertension and secondary polycythaemia.[28]

Role of Inflammation

COPD is defined as an inflammatory airways disease and in both asymptomatic smokers and patients with COPD, the inflammatory reaction in central and peripheral airways, as well as in the alveolar spaces and septae has been well characterised. In non-hypoxaemic patients with mild to moderate COPD, Peinado *et al*[29] observed that the number of inflammatory cells, largely constituted by T lymphocytes ($CD8^+$) was increased in PA of COPD compared with non-smokers and smokers with normal lung function. The intensity of the inflammatory infiltrate correlated with both the endothelium-dependent relaxation and the intimal thickness and was also abnormal in smokers with normal lung function. Thus, smoking-induced inflammatory changes may be important. Studies in murine model point to the role of the proinflammatory cytokine, IL-6 in pulmonary vascular remodelling.[30] In patients with COPD and PH, IL-6 levels were reported to be increased with those with genotype IL-6 GG and 5-HTT LL additively more likely to have PH.[31]

Endothelial Dysfunction

Endothelial damage and dysfunction as a consequence of tobacco smoking and/or chronic hypoxaemia has been proposed as the key initiating event in PH associated with COPD. The endothelium synthesises and releases a relaxing factor that has been identified as nitric oxide (NO).[32] NO production contributes to regulation of pulmonary perfusion depending on alveolar ventilation to assure optimised VA/Q distribution. NO regulates basal normoxic pulmonary vascular tone. It inhibits the thrombogenicity and proliferation of vascular smooth-muscle cells. Several studies have shown that nitric oxide plays an important role in the physiology of the lung.[33]

The endothelium has in recent years gained importance as an important regulator of vascular homeostasis, both in systemic and pulmonary vasculature. In patients with COPD, as in other forms of pulmonary hypertension, including idiopathic, the impairment of endothelial function may be associated with or result from changes in the expression or the balanced release of vasoactive mediators with vasodilator properties, such as NO or prostacyclin, and mediators with vasoconstrictive properties, such as endothelin-1 (ET-1) or angiotensin.[34]

Chronic hypoxaemia has been associated with endothelial dysfunction in pulmonary circulation in end-stage COPD. Endothelium-dependent pulmonary-artery relaxation *in vitro* was found impaired in arteries from patients with end-stage chronic obstructive lung disease. This was related to the degree of chronic hypoxaemia.[35,36] It was suggested that this may be due to impairment of NO synthase function by chronic

hypoxaemia.[37] Pulmonary hypertension was associated with diminished expression of endothelial nitric oxide synthase in secondary pulmonary hypertension, including in patients with COPD.[38] Reduced expression of endothelial nitric oxide synthase has been demonstrated in smokers with no or minimal airflow limitation.[39]

Low oxygen tension affects endothelial cellular physiology *in vivo* and *in vitro* in a number of ways, including the transcriptionally regulated expression of vasoactive substances and matrix proteins involved in modulating vascular tone or remodelling the vasculature and surrounding tissue. It results in the transcriptional induction of genes encoding vasoconstrictors and smooth muscle mitogens (PDGF-B, endothelin-1, VEGF, thrombospondin-1) and genes encoding matrix or remodelling molecules (collagenase IV (MMP-9), thrombospondin-1) and reciprocal transcriptional inhibition of vasodilatory or anti-mitogenic effectors (eNOS).[40]

However, evidence of endothelial dysfunction was presented even in patients with mild COPD. *In vitro* in PA rings obtained from lung specimens of mild COPD patients, endothelium-dependent relaxation-mediated by NO was reduced.[17] In the guinea pig, exposure to cigarette smoke induces selective endothelial dysfunction in pulmonary arteries, smooth muscle cell proliferation in small pulmonary vessels and reduced lung expression of eNOS.[41]

Besides impaired nitric oxide synthesis, other aspects of endothelial function have also revealed abnormalities in COPD. Prostacyclin is a major product of the cyclooxygenase pathway with potent vasodilatory and antimitogenic properties. Human emphysema lung tissue exhibited lower prostacyclin synthase expression within the pulmonary endothelium than in normal lung. Cigarette smoke extract (CSE) and aldehyde components suppressed prostacyclin synthase gene expression.[42] This imbalance in eicosanoid expression may contribute to vasoconstrictor response and vascular remodelling.

Endothelin-1 is a potent endothelium-derived vasoconstrictor peptide with important mitogenic properties. Pulmonary hypertension was associated with the increased expression of endothelin-1 in vascular endothelial cells of lung resection specimens from patients with idiopathic and different types of secondary PH including that in COPD. While there was a strong correlation between the intensity of endothelin-1-like immunoreactivity and pulmonary vascular resistance in the patients with plexogenic pulmonary arteriopathy, it was not observed in patients with secondary pulmonary hypertension.[43]

Right Ventricle and Left Ventricle in Pulmonary Hypertension

The right ventricle (RV) responds to increased PVR by gradually undergoing hypertrophy and later dilatation. Patients with stable COPD having moderate to severe airflow limitation without hypoxaemia have preserved right ventricular systolic function at rest. Concentric RV hypertrophy is the earliest sign of RV pressure overload in patients with COPD. This structural adaptation of the heart does not alter RV and left ventricle (LV) systolic function.[44] In 120 patients with severe emphysema evaluated for participation in the National Emphysema Treatment Trial[12], multiple stepwise regression revealed that arterial PO_2 was not an independent predictor of mean PAP. No correlation was found between indices of emphysema severity and PAP. Diastolic ventricular pressures were increased without evidence of systolic dysfunction. The effect on RV function cannot be predicted from PAP.

The right ventricular preload, afterload and contractility as well as its interaction with the LV, and the effects of intrathoracic pressure swings interact in a complex manner. The right ventricular dilatation serves to increase the end-diastolic volume (pre-load) and thus, maintains the cardiac output even as the right ventricular ejection fraction decreases. In severe emphysema, the low elastic recoil and less negative intrathoracic pressures compress the two ventricles into one another preventing dilatation of the RV and hence a decrease in the preload. This would eventually reduce the cardiac output. Lung volume reduction surgery (LVRS) improves the right ventricular systolic function.[45] It has been shown that LV function is impaired in patients with severe emphysema due to small end-diastolic dimensions. LVRS increases LV end-diastolic dimensions and filling, and improves LV function.[46] As the two ventricles are in series, the right ventricular output will affect the LV preload. An increase in RV end-diastolic volume due to its dilatation would shift the inter-ventricular septum into the LV. While this shift can reduce LV diastolic compliance and LV end-diastolic volume, the increased RV end-systolic pressure also serves to augment the LV emptying. Thus, the LV ejection fraction is relatively preserved even in advanced emphysema.[47] Sudden increases in PAP as occur on exercise, or during sleep and acute exacerbations can overwhelm the capacity of the RV to adapt to the increased afterload and precipitate right ventricular failure.

CLINICAL FEATURES

Symptoms due to PH are difficult to separate out from those due to COPD. Dyspnoea on exertion and exercise limitation are the major symptoms and alterations both in lung mechanics (airflow limitation and static and dynamic hyperinflation) and pulmonary haemodynamics contribute. Fatigue and chest pain (angina) suggest significant PH. As the disease progresses and right ventricular failure sets in, the well known manifestations of cor pulmonale – poor exercise tolerance, pedal oedema, cyanosis and abdominal

distension appear. Symptoms out of proportion to airways obstruction should lead to a suspicion of PH. Once diagnosed, the baseline evaluation of functional capacity in PH is done using the New York Heart Association (NYHA) classification, from classes I to IV.

Physical examination may reveal typical signs of airflow limitation and hyperinflation due to COPD. Signs specific to PH are those of cor pulmonale – accentuated P2, left parasternal heave, increased jugular venous pressure, pedal odema, midsystolic murmur over pulmonary valve, right-sided S4 gallop, hepatojugular reflux with pansystolic murmur of tricuspid regurgitation and ascitis. Falling cardiac output causes hypotension and cold extremities. Without signs of cor pulmonale, PH cannot be recognised clinically. It should, however, be noted that the signs may be modified by the degree of hyperinflation. Moreover, as mild to moderate PH is far more common than severe or out-of-proportion PH, classical signs of PH are uncommon in COPD. Thus, physical examination has poor sensitivity to diagnose PH.

In moderate stages of COPD, exercise-induced desaturation may occur and in advanced disease with chronic hypoxaemia, cyanosis may be apparent. Patients with predominant emphysema may not develop clinically manifest cor pulmonale. As cardiac output falls further, easy fatigability and occasionally syncope follow. The sequence of worsening VA/Q matching, increasing respiratory failure with appearance of hypercapnia and falling cardiac output eventually terminates fatally.

DIAGNOSTIC EVALUATION

Spirometry

Spirometry with response to inhaled bronchodilator is the standard investigation for the diagnosis and staging of severity of COPD. However, FEV_1 bears only a poor or a modest relationship with the degree of PH[11,12] and therefore cannot be used to predict the possibility of raised PAP. However, most cases of moderate to severe PH would be associated only with advanced COPD. PH does not affect spirometric parameters to any major extent although some reduction in the forced vital capacity may occur.

Chest Radiography

A plain PA chest radiograph is usually obtained as part of the initial diagnostic work-up in a patient with COPD and may provide evidence of PH in addition to the signs of hyperinflation. Enlarged main and hilar pulmonary arterial shadows with peripheral vascular pruning are suggestive of PH. The Hilar-thoracic (HT) index[48] and width of the descending branch of the right pulmonary artery (DRPA),[49] measured at its widest point near the bifurcation of the artery from the right middle lobe and above the branching of the middle basilar artery, have been found to be useful in predicting the presence of PH and have been validated against RHC. Lupi *et al*[48] introduced the HT index and observed that a value of greater than 38% identified 74% patients with PAH. Teichmann *et al*[49] observed that a diameter of 18mm or more of the DRPA identified 72% of patients of chronic bronchitis with PAH with 7.4% false positives. Chetty *et al*[50] reported that a value for the hilar thoracic ratio of 35% or more was 95% sensitive and 100% specific for presence of pulmonary hypertension in COPD patients. Chhabra *et al*[51] have validated these measurements against MPAP measured by color Doppler echocardiography. The two radiological indices were highly correlated with each other. Increased HT index and increased width of the DRPA had a 100% specificity and predictive value positive (PVP) in identifying patients with pulmonary hypertension. However, sensitivity and predictive value negative (PVN) were low. As the specificity is far greater than sensitivity, mild PH would not be detected radiologically. However, when the signs are positive, it is likely to be a clinically significant PH. A chest radiograph is also a simple and economical tool to follow the course of the disease.

Electrocardiogram (ECG)

An ECG has low sensitivity for PH but a good specificity exceeding 80%.[52] Therefore, milder degrees of PH are not likely to produce any abnormality. However, presence of one or more of the following signs points to the likely presence of clinically significant PH. Serial ECGs over time are useful to detect the onset of significant PH.

A right-axis deviation, right bundle-branch block, tall R and R/S>1 in V1 with large S and small R and R/S < 1 in V5 or V6, a qR pattern in V1 are all suggestive of right ventricular hypertrophy while tall (>2.5mm), narrow and pointed P waves in II, II and aVF suggest right atrial enlargement. In addition to these signs, an ECG may provide evidence of co-existing left heart disease or myocardial ischaemia.

Echocardiogram (ECHO)

The echocardiogram (ECHO) is the initial screening tool for PH. Being non-invasive, it also serves as a useful monitoring tool. However, it is operator-dependent and therefore, between-operator variability may be large. Identification of a tricuspid regurgitation (TR) jet on Doppler ECHO allows calculation of right ventricular systolic pressure (RVSP) by first estimating right ventricular pressure by modified Bernoulii equation ($4v^2$, where v=TR jet velocity in m/s) and adding to it the right atrial pressure, determined by ECHO examination of the inferior vena cava. In the absence of pulmonary artery outflow obstruction, PAP is approximately equal to RVSP.

The limitations of ECHO, besides being operator-dependent, are an inability to detect a TR jet in about a third of patients due to hyperinflation or rotation of the heart. There is a good correlation between RVSP and RHC pressures. However, RVSP estimated by ECHO was also inaccurate, being within 10mmHg of RHC measurements in only about 48% of patients in one study. The inaccuracy increased with increasing hyperinflation.[53,54] Recently, Fisher *et al*[55] reported that while overestimation and underestimation was noted with similar frequency, the magnitude of underestimation was more. In spite of these limitations, non-availability of RHC at most centers as well as its invasive nature make ECHO as the most commonly used diagnostic modality for PH. A careful examination by an experienced operator can improve the accuracy and utility.

ECHO examination also provides information about systolic and diastolic function of the left heart as well as valvular and wall motion abnormalities due to ischaemia. These may contribute to PH (WHO Group 2). Besides, a functional assessment of the right ventricle can be carried out. Very often, it is the ability to adapt to increasing PAP that determines the course of PH rather than the absolute values of the former. The Tei index and tricuspid annular displacement have been found to predict survival of patients with idiopathic PAH.[56-58] The clinical value of these measurements of right ventricular dysfunction in COPD has not been established.

Other Pulmonary Function Tests and Arterial Blood Gases

The next step should be to obtain measurements of static lung volumes to better characterise the physiological derangements in COPD and also measure the diffusion capacity. Diffusion capacity may be reduced both because of emphysema as well as PH. This should be followed by an arterial blood gas measurement to confirm a diagnosis of respiratory failure. Most stable patients of COPD with significant PH will have a compensated chronic respiratory acidosis with hypoxaemia and hypercapnia. It must be emphasised that although the likelihood of hypoxaemia is greater in patients with moderate or severe PH as compared to mild, the correlation of arterial blood gas abnormalities with the degree of elevation of PAP is not strong. If the symptoms are out of proportion to the derangements of lung mechanics or there is severe hypoxaemia or severely reduced carbon monoxide diffusing capacity, one should suspect PH.[26,59]

6-Minute Walk Test

A 6-minute walk test (6-MWT) is a simple, safe, and reproducible test that is representative of daily activities. It should be used for a baseline assessment, to follow the progress of the disease and to assess the response to treatment. It is an often used objective outcome parameter in research. A properly carried out 6-MWT as per the standardised procedure of the American Thoracic Society[60] noting the fall in oxygen saturation as well as the blood pressure and pulse rate response is a very useful test for the above reasons.

Right Heart Catheterisation (RHC)

Right heart catheterisation (RHC) is the gold standard to diagnose PH. It allows accurate measurements of MPAP, and also PCWP to determine the contribution of pulmonary venous hypertension. Pulmonary vascular reactivity to vasodilators can be assessed. However, its invasive nature with a small but definite risk and limited availability makes it an infrequently tool, especially in resource-poor countries. Its clinical utility in patients of COPD with PH has not been evaluated.

Brain-type Natriuretic Peptide (BNP)

There is some evidence that B type BNP may be a useful biomarker for PH in patients with COPD. Patients with cor pulmonle had a higher mean BNP level compared to those without it and the BNP levels correlated with PAP on echocardiography.[61] Gemeci *et al*[62] reported an increase in BNP levels after treadmill exercise in patients with COPD having normal ventricular function at rest. In another recent study, Inoue *et al*[63] found a significant correlation between plasma BNP level and % ejection fraction and pulmonary artery systolic pressure on echocardiography in patients with COPD and suggested it as a non-invasive biomarker that can be used as a screening parameter for latent PH and left ventricular dysfunction. However, due to substantial overlaps with normal subjects, the clinical utility if measuring BNP levels has not been established.

Other Investigations

Patients of PH with out-of- proportion elevation in PAP require further investigations to exclude other additional causes of PH before attributing it to COPD. A computed tomographic (CT) examination including CT angiography, if required, VA / Q scans and pulmonary angiography to rule out chronic thromboembolic pulmonary hypertension, polysomnography for suspected cases of obstructive sleep apnea, and consideration of other causes of PAH (WHO Group 1) may be required.

PROGNOSIS

Pulmonary artery pressures are one of the most significant prognostic factors in severe COPD. In a study of prognostic indicators, other than age and the severity of airways obstruction after administration of bronchodilator, patients less than 65 years of age had a

poorer prognosis in the presence of cor pulmonale.[64] Pulmonary artery pressures greater than 20mmHg obtained by RHC were found to significantly predict mortality at 5 years[10]. In patients with an initial RHC PAP of 25mmHg or less, the 5-year survival was of 62% *vs* 36.3% in the remainder. Further, the best prognostic factor in COPD patients receiving LTOT was found to be the level of PAP rather than the degree of airways obstruction or abnormalities of arterial blood gases.[65]

Pulmonary artery pressure worsens at the rate of 0.4mm to 2.8mm per year.[15,66,67] The change of PAP during a 7-year follow-up was found to be correlated with the change of arterial oxygen tension (PaO_2), the more PaO_2 worsened the more PAP increased.[15] Long term oxygen therapy (LTOT), as discussed in the following section, decreases the rate of worsening or stabilises it but does not reverse it.[66,67]

TREATMENT

It is generally agreed that in patients with PAP < 35mmHg, specific therapy for PH is not required.[24] Standard therapy of COPD with inhaled bronchodilators supplemented with corticosteroids, regular sessions of pulmonary rehabilitation including nutritional supplementation, and influenza vaccination remain the cornerstone of management. The need for oxygen therapy is guided by the levels of PaO_2 rather than the levels of PAP in these patients. However, in those patients with severe or out-of-proportion PH, it is not known if oxygen therapy is sufficient to reverse or arrest the vascular changes. Endothelial dysfunction, as discussed above, may play a critical role in the pathogenesis of PH. The balance of vasoactive mediators with vasodilator properties, such as NO or prostacyclin, and mediators with vasoconstrictive properties, such as endothelin-1 (ET-1) is altered due to endothelial dysfunction. Therefore, therapies such as [prostanoids, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors] may offer an option.[68]

However, all the studies carried out so far with these drugs have been uncontrolled or have been carried out in very small number of patients. The evidence in favour of these drugs is equivocal.

Long Term Oxygen Therapy (LTOT)

To date, long-term oxygen therapy is the treatment of choice in COPD patients with PH and hypoxaemia because it slows or reverses its progression. Long term oxygen therapy in well-defined patients with chronic hypoxaemia with PH has been shown to confer survival benefit in COPD. This was demonstrated in two well-known studies - the Nocturnal Oxygen Therapy Trial (NOTT)[69] and the and Medical Research Council (MRC).[66] Oxygen therapy given continuously for > 18 hours per day was shown to prevent deterioration or even reduce PAP at rest and on exercise after 6 months to 1 year. In the study by Weitzenblum *et al*[67], a reversal of the progression of PH was observed under LTOT. Zielinski *et al*[70] reported stabilisation of PAP on 15 hours a day of LTOT.

While these studies have been carried out in small number of subjects, the beneficial effects have been fairly consistent leading to a consensus on LTOT. In the presence of PH and signs of cor pulmonale, a PaO_2 between 55 to 59mmHg demonstrated in a stable condition at an interval of 4 weeks is an indication for LTOT. Further, the greater the daily duration of application, greater is the benefit and a usage of at least 15 to 18 hours a day is recommended. In anticipation of a nocturnal worsening of hypoxaemia, an increase in the flow rate of 1 LPM is also recommended.

The issue of isolated nocturnal hypoxaemia in the absence of sleep apneas is another debatable aspect of LTOT. Patients with COPD who have normal oxygen saturation during the daytime but desaturate at night during sleep may be more prone to develop PH. Thus, these too may be theoretically candidates for LTOT. Fletcher *et al*[71] observed that the nocturnal desaturator group who received supplemental oxygen during sleep over 36 months showed a significant downward trend in PAP (-3.7mmHg) compared with desaturating patients treated with room air (+3.9mmHg). In another study[72], two year nocturnal oxygen therapy (NOT) did not modify the evolution of pulmonary haemodynamics and also did not allow delay in the prescription of LTOT. The PAP increased at the same rate in those who received NOT compared to those who did not. No effect of NOT on survival was observed. Both these studies have included a small number of subjects and the variable results do not provide any justification for NOT in patients of COPD with normal daytime saturation and nocturnal desaturation.

Vasodilators

Vasodilators have been used in the treatment of PH but with disappointing results. These are not recommended because of their potential detrimental effects on gas exchange, produced by the inhibition of hypoxic pulmonary vasoconstriction and their lack of effectiveness after long-term treatment.

Urapidil is a vasodilator that acts by postsynaptic alpha 1-blockade while inhibiting the aortic pressure baroreceptor reflex and reducing central sympathetic tone. In a study on 10 patients given intravenous urapidil for two days, Adnot *et al*[73] observed a decrease in PAP and PVR with much less effects on systemic pressures and resistance. It also maintained the heart rate nearly constant and only slightly increased the cardiac index. It has not been used in patients of COPD developing PH. In ten patients of COPD with PH, 30mg Nifedipine given for 18 months, no significant modification in heart rate, mean pulmonary pressure,

mean arterial pressure or blood gases was observed. On the other hand, a decrease in cardiac output was found.[74]

Nitric Oxide (NO)

Nitric oxide induces vasodilatation by increasing cyclic guanosine monophosphate (cGMP) levels in vascular smooth muscles and is an important physiological regulator of both pulmonary and systemic vascular tone.[75] NO administered by inhalation through a nasal canula at a dose of 25 parts per million for 24 hours with oxygen, reduced PVR without significant change in mean PAP.[76] Pulsed inhaled NO plus oxygen over three months decreased PVR, mean PAP, and increased cardiac output without worsening oxygenation.[77]

Thus, while the beneficial effects of nitric oxide on pulmonary haemodynamics have been demonstrated, the clinical utility in PH associated with COPD has not been explored.

Other Drugs for PH and Cor-pulmonale

Use of diuretics is common and also useful in patients with peripheral oedema as well as those who have a left ventricular diastolic dysfunction contributing to PH in patients with COPD. The beneficial effect is due to a decreased preload. However, excessive dieresis may be harmful, especially in patients with a reduced cardiac output because an adequate preload is essential for adequate RV performance. Digoxin may be of some use in right heart failure especially if there are supraventricular arrhythmias. Its effect is however less predictable than in left ventricular failure.

Targeted Therapy

The recognition of the role of endothelial dysfunction in idiopathic PH has led to development of specific agents targeted to address it. The targets are the nitric oxide, prostacyclin and endothelin pathways. As discussed above, endothelial dysfunction has also been recognised in PH associated with COPD. Therefore, there is great interest in the use of these drugs in COPD as well. However, there are no large-scale randomised controlled trials with any of these agents. At present, the use of specific PAH therapy in COPD patients with moderate PH is discouraged because of the potential detrimental effect of some of these drugs on gas exchange and there are no data demonstrating their efficacy. A cautious application of these drugs in severe and out-of-proportion PH in COPD may be justified, preferably in the setting of a clinical trial. The limited studies carried out so far are reviewed below.

Prostacyclin

Prostacyclin is an endogenously produced pulmonary vasodilator. In a study by Archer and colleagues,[78] prostacyclin infusion for 48 hours in mechanically ventilated COPD patients with PH and acute respiratory failure showed no significant benefit. PaO^2 dropped in patients receiving prostacyclin infusion compared to placebo group. Prostacyclin can increase intrapulmonary shunting causing lower systemic oxygen saturation. However, increased right ventricular output by prostacyclin may counterbalance the increased shunting.

Another drug, cicletanine enhances endogenous prostacylin production. Saadjain and colleagues[79] administered cicletanine (50mg daily) for 12 months to COPD patients with PH. In this small study, cicletanine resulted in a reduction of mean PAP and PVR after three and 12 months of treatment. There was a small but a non-significant reduction of PaO_2.

Sildenafil

Sildenafil is a phosphodiesterase inhibitor that has been used with some success in idiopathic PH. Phosphodiesterase (PDE) inactivates cGMP, the second messenger of the prostacyclin pathway. The majority of PDE present in the lungs is PDE5. PDE5-inhibition blocks the degradation of cGMP and enhances the vasodilatory action of cGMP.[80]

In six patients with severe COPD, effects of injection of 50mg sildenafil intravenously and a 3-month period of oral sildenafil therapy 50mg twice daily were evaluated.[81] Intravenous sildenafil reduced PAP and PVR significantly on RHC. And after 3 months of oral sildenafil, the mean PAP and PVR had decreased significantly. The 6-min walk distance increased by 82m.

In another study, a favourable but non-uniform effect of 50mg three times daily sildenafil given for 8 weeks was observed on PAP and right ventricular systolic pressure in a small group of 6 patients with advanced COPD.[82] Fifteen stable COPD patients (GOLD stage II-IV) underwent right heart catheterisation at rest and during exercise before and after a 3-month treatment with sildenafil. Nine of these patients had PH. Treatment with sildenafil had no effect on stroke volume or exercise capacity.[83] Regardless of MPAP at rest, a 50mg single dose of sildenafil attenuated the increase in PAP during submaximal exercise in COPD. This attenuated increase was neither accompanied by enhanced SV and CO, nor by improved maximal exercise capacity.[84] At present, there is insufficient evidence to recommend the use of sildenafil in patients of COPD with PH.

Endothelin Antagonists

Endothelin-1 is a powerful vasoconstrictive agent produced by vascular endothelium and plays a major role in vascular homeostasis. Blockage of endothelin receptor leads to pulmonary vasodilation. Bosentan has been used with good results in idiopathic PH. In

patients with COPD and PH, there have been two recent studies using this drug.

In a double-blind, placebo-controlled study,[85] 30 patients with severe or very severe COPD were randomly assigned to receive either bosentan or placebo for 12 weeks. Compared with placebo, patients treated with bosentan during 12 weeks showed no significant improvement in exercise capacity as measured by the 6-min walking distance and there was also no change in lung function, PAP, maximal oxygen uptake or regional pulmonary perfusion pattern. In contrast, arterial oxygen pressure dropped, the alveolar-arterial gradient increased and quality of life deteriorated significantly in patients assigned bosentan. Thus, it produced more harm than good.

In another study[86], bosentan was administered to 16 patients for a period of 18 months. It resulted in a significant improvement of PAP and pulmonary vascular resistance and improved exercise capacity measured by 6-MWT. The effect was most striking in the 30% of patients in GOLD stage III and IV. Most patients in stage IV did not improve, but in all patients the treatment stopped the progressive worsening of haemodynamics over time.

The results in the above studies are contradictory and large scale randomised controlled studies are required before the indications for use of bosentan in COPD can be defined. At present, there is not enough evidence to recommend its use.

It must be pointed out that patients with COPD often have significant comorbidities. Several of these conditions can produce an additional component of PH. Indeed, ischaemic heart disease, hypertensive cardiomyopathy, chronic heart failure and worsening of chronic respiratory failure due to obesity and obstructive sleep apnea are frequently encountered. These require specific management.

CONCLUSIONS

Pulmonary hypertension in patients with COPD appears to be an early event that may develop and progress in parallel with physiological derangements of the airways and lung parenchyma. Chronic hypoxaemia plays a major role in amplifying the process of pulmonary vascular remodelling and endothelial dysfunction that are critical to the pathogenesis of PH. Most patients with PH have only mild to moderate elevations in PAP and do not require specific therapy. A small subset of patients however develops severe PH that is often out of proportion to alterations in lung mechanics and blood gas abnormalities. This phenotype of COPD requires better characterisation. Newer insights into the role of endothelial dysfunction in the development of PH in patients with COPD and proven benefit of therapy targeted to correct the consequences of endothelial dysfunction in idiopathic PH has spurred efforts to examine whether these drugs will offer any benefit to patients with COPD who develop severe PH. So far, the evidence in favour of these drugs is not strong. Hence, these should be used carefully in selected patients, and preferably in the settings of a clinical trial and the patients should be carefully monitored as some may even deteriorate. Severe PH in COPD carries a poor prognosis. At present, LTOT is the only therapy that has been shown to confer survival benefit.

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