COMPREHENSIVE ASSESSMENT OF COR PULMONALE IN COPD

Naveena.B[1*], Melwinraj.A[1], Pratheesh Xavier.P[1], Narmatha.M[1], Thirupathi Kumaresan.P[2]
[1]Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnan koil – 626126, Srivilliputur, Tamil Nadu, India.
[2]Professor, Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Krishnan koil, Tamil nadu -626126

Abstract:
In 1963, an expert committee of the World Health Organization defined cor-pulmonale as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs...,"but this pathological definition is in fact of limited value in clinical practice. Mild-to-moderate pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD); such a complication is associated with increased risks of exacerbation and decreased survival. Habitual lung conditions as well as conditions of the pulmonary vessels beget increased pulmonary vascular resistance. The most common beginning medium causing increased pulmonary blood pressure (pulmonary hypertension) is by pulmonary vasoconstriction, activation of coagulation pathway and annihilation of pulmonary arterial vessels. Pulmonary hypertension causes pressure load on the right ventricle and hence right ventricular blowup. Originally, there's right ventricular hypertrophy, but as cardiac decompensation sets in and right heart failure ensues, dilatation of right ventricle occurs. In patients with COPD, clinical signs may be masked by lung hyperinflation. Most patients initially have dyspnea, which becomes more severe as right ventricular failure occurs. Chest pain may occur and be difficult to differentiate from angina pectoris. In patients with severe COPD, orthopnea, worsening right ventricular function, bloating and early satiety occurs. The goal of treatment is to control symptoms. It is important to treat medical problems that cause pulmonary hypertension, because they can lead to Cor- pulmonale. As per NICE (National Institute for Health and Care Excellence) guidelines, the treatment of Cor pulmonale is Long Term Oxygen Therapy.
Key words: *Cor-pulmonale, Pulmonary hypertension, COPD, Oxygen, pulmonary arterial pressure*

Corresponding author:
Naveena.B,
AKCP,
Krishnan koil, Virudhunagar,
Tamil Nadu - 626 126
E-Mail: *navee.baburaj@gmail.com*
Phone No.: *8870810097*

QR code

INTRODUCTION:

The term"cor pulmonale" is still popular in the medical literature, but there is presently no consensualdefinition. In 1963, an expert committee of theWorld Health Organization defined cor pulmonaleas"hypertrophy of the right ventricle resulting fromdiseases affecting the function and/or structure of thelungs...,"[1] but this pathological definition is in fact oflimited value in clinical practice. As pulmonaryhypertension (PH) is the"sine qua non"of cor pul-monale[2].We believe that the best definition of corpulmonale ispulmonary arterial hypertension resulting from diseases affecting the structure and/or the function of the lungs; pulmonary arterial hypertension results in right ventricular enlargement (hypertrophy and/or dilatation) and may lead with time to right heart failure [3].Pulmonary hypertension in COPD is placed in group 3 of the 2003 WHO classification of PH, i.e., PH associated with disorders of the respiratory system and/or hypoxemia. PH associated with lung disease is defined as resting mean PAP (mPAP) greater than 20 mm Hg, which is different from the definition of primary pulmonary hypertension (mPAP >25 mm Hg) [4].

A new diagnostic classification of pulmonary hypertension was developed by a group of experts in 1998[5] and is presented on Table1.

New diagnostic classification of pulmonary hypertension [5]

1. Pulmonary arterial hypertension
1.1 Primary pulmonary hypertension
(a) Sporadic
(b) Familial
1.2 Related to:
(a) Collagen vascular disease
(b) Congenital systemic to pulmonary shunts
(c) Portal hypertension
(d) HIV infection
(e) Drugs/toxins
(1) Anorexigens
(2) Other
(f) Persistent pulmonary hypertension of the newborn
2. Pulmonary venous hypertension
2.1 Left sided atrial or ventricular heart disease

2.2 Left sided valvar heart disease	
2.3 Extrinsic compression of central pulmonary veins	
(a) Fibrosingmediastinitis	
(b) Adenopathy/tumours	
2.4 Pulmonary veno-occlusive disease	
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia	
3.1 Chronic obstructive pulmonary disease	
3.2 Interstitial lung disease	
3.3 Sleep disordered breathing	
3.4 Alveolar hypoventilation disorders	
3.5 Chronic exposure to high altitude	
3.6 Neonatal lung disease	
3.7 Alveolar capillary dysplasia	
4. Pulmonary hypertension caused by chronic thrombotic and/or embolic disease	
4.1 Thromboembolic obstruction of proximal pulmonary arteries	
4.2 Obstruction of distal pulmonary arteries	
(a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)	
(b) In situ thrombosis	
(c) Sickle cell disease	
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature	

5.1 Inflammatory	
(a) Schistosomiasis	
(b) Sarcoidosis	
5.2 Pulmonary capillary haemangiomatosis	

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide with an increasing prevalence during the past decades. Mild-to-moderate pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD[6].

In our opinion cor pulmonale corresponds to the third part of this classification and must be distinguished from pulmonary venous hypertension (part 2), and also from primary pulmonary hypertension (part 1) and from thromboembolic pulmonary hypertension (part 4) [7].

PATHOPHYSIOLOGY
Habitual lung conditions as well as conditions of the pulmonary vessels beget increased pulmonary vascular resistance. The most common beginning medium causing increased pulmonary blood pressure (pulmonary hypertension) is by pulmonary vasoconstriction, activation of coagulation pathway and annihilation of pulmonary arterial vessels. Pulmonary hypertension causes pressure load on the right ventricle and hence right ventricular blowup. originally, there's right ventricular hypertrophy, but as cardiac decompensation sets in and right heart failure ensues, dilatation of right ventricle occurs [8].
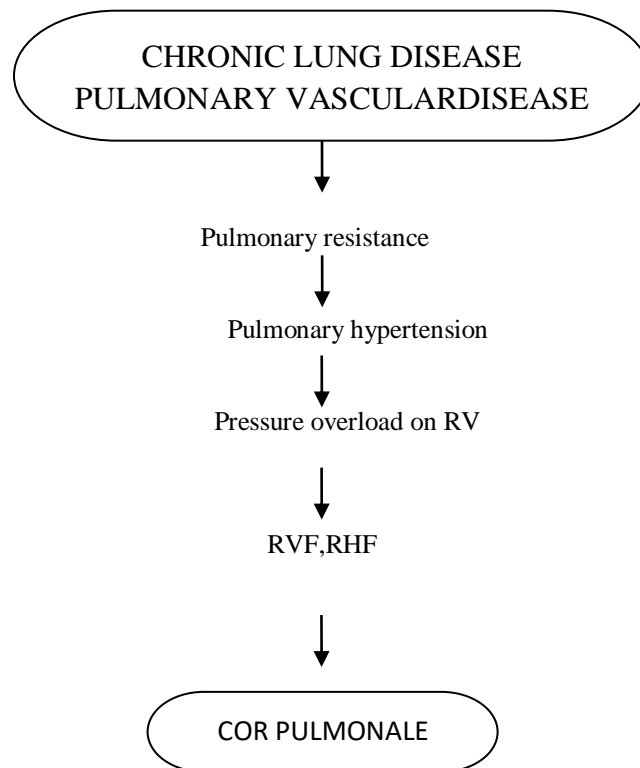
CHRONIC LUNG DISEASE
PULMONARY VASCULARDISEASE

↓

Pulmonary resistance

↓

Pulmonary hypertension

↓

Pressure overload on RV

↓

RVF,RHF

↓

COR PULMONALE

Figure;1 Pathogenesis of corpulmonale

The walls of the large pulmonary highways are thinner than those of the systemic highways and are designed to distend. The pulmonary vessels have lower resistance than their systemic counterparts, and the pulmonary arterioles can alter their quality in response to changes in blood volume.

In healthy persons, the cardiac affair of the right ventricle has to increase by2.5 times its birth value to produce any elevation in PAR Pulmonary vascular resistance (PVR) depends on flux pressure in the pulmonary roadway, exodus pressure in the pulmonary modes or left patio, and blood inflow through the lungs. Because the pulmonary circuit is typically a low- resistance, largely biddable system, significant PAH develops only in cases with considerable abnormality of the pulmonary vessels.

In grown-ups, the right ventricle is a thin- walled, crescent-structured chamber that's further of a volume pump than a pressure pump and adapts better to changing preloads than to acute increases in afterload. Still, some investigators have set up a reduced caravan ejection bit (RVEF) [9,10]. An addition of the caravan afterload, performing from increases in PAP and PVR, is the most common cause of reduced RVEF.

Several mechanisms have been included in the pulmonary Hypertension in COPD.

Pulmonary Vasoconstriction
Hypoxic condensation of the small muscular pulmonary highways [11] is a defensive medium to divert blood inflow from hypoxic alveoli to more voiced alveoli and reduce ventilation- perfusion mismatch [12]. Still, when alveolar hypoxia is verbose, similar as in severe COPD, it causes generalized pulmonary vasoconstriction and accordingly raises the PVR.patient hypoxia leads to pulmonary vascular redoing [13] which contributes to the PVR.

Pulmonary Vascular remodeling
Vascular remodeling in COPD cases is seen at all stages of the complaint and is characterized by intimal fibrosis and proliferation of longitudinal smooth muscle in the muscular pulmonary highways and arterioles, and neomuscularization of pulmonary arterioles [14-16]. These pulmonary vascular changes also do in cases with mild COPD. This suggests that mechanisms other than hypoxia also play an important part in the pathogenesis of vascular remodeling[17].

Still, pathologic studies in COPD haven't shown complex lesions, which are constantly encountered in cases with pulmonary arterial hypertension [18], similar as plexiform lesions or angiomatoid lesions, characteristic of severe PH.

Endothelial Dysfunction
The normal endothelium plays an important part in modulating pulmonary vasomotor tone and cellular proliferation. Nitric oxide (NO) produced by endothelial NO synthase (eNOS) has vasodilator and antiproliferative parcels. Prostacyclin produced by the exertion of prostacyclin synthase is another vasodilator that also protects against vascular redoing. fighting vasodilatation is endothelium-deduced endothelin- 1 (ET- 1). In cases with COPD and PH there's a reduction in the conflation and/ or release of NO from the lung [19]. In COPD there's a reduction in the expression of prostacyclin synthase mRNA[20], and in cases with secondary pulmonary hypertension there's an inordinate expression of endothelin-1 (ET-1) [21]. Arterial ET- 1 also increases shortly after occurrences of nightly oxygen desaturation in cases with COPD and remains advanced during the day in these subjects [22].

Inflammation
Cigarette smoking induces a CD8 T- lymphocyte infiltration of the adventitia of muscular pulmonary highways, which correlates with both the endothelium-dependent relaxation and the intimal consistence, suggesting the implicit involvement of an seditious process in the pathogenesis of pulmonary vascular abnormalities in the early stage of COPD [23].Systemic inflammation is a given element of COPD [24,25] and inflammation may contribute to the pathogenesis of PH. [26] showed that elevated circulating situations of the proinflammatory cytokine interleukin- 6 (IL- 6) directly identified with elevations in Mpap($r = 0.39$; $P < 0.001$). also, C-reactive protein situations have also been shown to relate with both PAP and situations of ET- 1 [27].

Destruction of the Pulmonary Vascular Bed
Destruction of the pulmonary vascular bed by emphysema reduces the total cross-sectional area of the pulmonary circulation and increases the total PVR when the remaining capacitance vessels are abnormal and unable to accommodate the increased diverted pulmonary blood flow at rest and the increased CO during exercise.

A hypercoagulable state has also been described in patients with COPD [28,29]. There appears to be an increased frequency of deep venous thrombosis and pulmonary embolism in acute exacerbations of COPD [30-32] and histopathologically thrombotic lesions have been detected in lung tissue from patients with severe emphysema undergoing lung-

volume reduction surgery [33]. It is postulated that the inflammatory aspects of the so-called COPD exacerbation may trigger a hypercoagulable state and increase the risk of thrombosis including in situ thrombosis.

Polycythemia
Polycythemia not only increases the viscosity of blood and the resistance to blood flow through the pulmonary circulation [34] but also augments hypoxic pulmonary vasoconstriction by causing a local deficiency of NO which may be related to the excessive removal of NO from the pulmonary circulation by the large amount of hemoglobin [35,36].

Genetic Factors
The pulmonary vascular response to hypoxia is genetically determined. Serotonin (5-hydroxytryptamine, 5-HT) and its transporter (5-HTT) play a role in pulmonary artery smooth muscle cell (PASMC) proliferation and vascular remodeling. The severity of PH in hypoxic COPD patients depends upon 5-HTT gene polymorphism. PH is most severe in patients carrying the LL genotype, which is associated with higher levels of 5-HTT expression in PASMCs [37]. ACE is present in very high concentrations in the lungs and its activity is further increased by hypoxia [38]. ACE is a vasoconstrictor and mediator of PASMC proliferation. The ACE DD genotype is associated with increased circulating and tissue concentrations of ACE. Moreover, the ACE DD genotype is associated with exaggerated PH during exercise in COPD patients [39].

Hyperinflation
Severe emphysema with air-trapping and hyperinflation is associated with intrinsic positive end-expiratory pressure of 5–7.5 cm H2O [40]. The positive alveolar pressure throughout respiration contributes to the high PVR [41] aswell as increases both PAWP and PAP. This mechanism may assume a more important role in development of PH during exercise and in patients with severe emphysema who are not hypoxemic.

DIAGNOSIS OF COR PULMONAL
Symptoms and physical signs are of little help in the diagnosis of cor pulmonale. Dyspnea on exertion and fatigue is generally present in advanced chronic respiratory disease with or without PH. In COPD, they are essentially the consequence of airflow limitation and hyperinflation rather than PH. Physical signs that are observed in severe PH and particularly in IPAH [e.g., pansystolic murmur owing to tricuspid regurgitation (TR)] are rarely present in respiratory patients with PH. This can be explained by the modest degree of PH in most patients and by the late occurrence (or no occurrence at all) of RHF. Peripheral edema occurs rather late in the course of chronic respiratory disease, particularly COPD, and is not synonymous with RHF [42,43].

The width of the right descending pulmonary artery on the chest radiograph may indicate the presence of pulmonary hypertension. A width of > 16 mm has been shown to correlate with the presence of pulmonary hypertension in patients with COPD[44]. In patients with COPD, a high cardiothoracic ratio is highly sensitive and 100% specific for the presence of pulmonary hypertension [45]. Although the chest radiograph may provide evidence for the presence of pulmonary hypertension, it cannot measure the degree of pulmonary artery pressure elevation. A globular heart may indicate right ventricular dilation or hypertrophy, which would be further supported by the presence of a decrease in the retrosternal air space on a corresponding lateral view. Electrocardiographic evaluation for right ventricular hypertrophy is highly specific but not sensitive [46].

Magnetic resonance imaging may prove useful for the diagnosis of PH and altered right ventricular structure and function. The non-invasive diagnosis of PH is presently based on Doppler echocardiography, which is by far the best method [47].The maximum velocity of the TR jet allows the calculation of the right ventricle– right atrial pressure gradient by applying the Bernoulli equation. In COPD patients, hyperinflation makes echocardiography difficult and a reliable examination cannot be obtained in more than 60–80% of the cases [14]. PAP measured invasively has not always been confirmed in COPD patients and a mean error of estimate for systolic PAP of about 10 mmHg has been reported [48].

Computed tomography (CT) can be used to determine the pulmonary artery cross-section diameter, which correlates well with pulmonary artery pressure [49].High-resolution CT scans (HRCT) can provide evidence of parenchymal disease. Magnetic resonance imaging (MRI) is becoming the reference standard for measuring ventricular dimensions because it provides the best image of the right ventricle [50].

Severe exacerbations of chronic respiratory disease, occurring in patients with chronic respiratory failure, are characterized by a worsening of hypoxemia and hypercapnia and simultaneously there is a pronounced increase in PAP[51]

A right heart catheterisation is a gold standard for diagnosis, assessment of Pulmonary hypertension severity. Right heart catheterization reveals evidence of right ventricular (RV) dysfunction without left ventricular (LV) dysfunction, which is an estimation of left atrial pressure. Thus, RV dysfunction is also defined as having a PCWP below 15 mmHg.

PFTs and 6-minute walk test for assessment of the severity of lung disease and exercise capacity respectively[52].

Plasma brain natriuretic peptide (BNP) may provide a reliable and accurate diagnostic test for PH. BNP is a cardiac hormone, which is synthesized by the ventricle and secreted into the circulation in response to increased wall stretch and tension during elevations in end-diastolic pressure [53].

DIFFERENTIAL DIAGNOSIS
- Atrial myxoma
- Chronic thromboembolic pulmonary hypertension
- Congestive (biventricular) heart failure
- High-output heart failure
- Infiltrative cardiomyopathies
- Obstructive sleep apnea (OSA)
- Pulmonary hypertension
- Right heart failure due to congenital heart diseases
- Right heart failure due to right ventricular infarction [52].

SYMPTOMS AND SIGNS
The symptoms of chronic cor pulmonale develop gradually over years. Most patients initially have dyspnea, which becomes more severe as right ventricular failure occurs. Chest pain may occur. In patients with severe COPD, orthopnea is common and is thought to be related to the effect of lung hyperinflation on venous return to the right side of the heart.[54].

Sodium retention is enhanced by hypercapnia and ameliorated by long-term oxygen therapy in hypoxemic patients.[55] True right heart failure is characterized by raised jugular venous pressures, congestive hepatomegaly as well as peripheral edema[52].Hyperinflation reduces the yield of cardiac auscultation for the classic signs of PH and CP i.e,loud P_2, S_3 gallop, the systolic murmur of tricuspid regurgitation [56].

The main characteristic of pulmonary hypertension in chronic respiratory disease is probably its mild to moderate degree of hypertension, with resting PAP in a stable state of the disease ranging usually between 20–35 mm Hg. Its well-recognized in COPD is very

different from left heart disease, congenital heart disease, pulmonary thromboembolic disease. [57].

Probably the most important clinical symptom of pulmonary hyper-tension is fatigability; the most characteristic symptom of heart failure, dyspnea[58].

TREATMENT

The goal of treatment is to control symptoms. It is important to treat medical problems that cause pulmonary hypertension, because they can lead to Cor-pulmonale. As per NICE (National Institute for Health and Care Excellence) guidelines, the aim in the management of pulmonary hypertension and cor pulmonale is to reduce the frequency of episodes of RHF (Right Heart Failure).

FOR PULMONARY HYPERTENSION

Phosphodiesterase-5 Inhibitors

1. Sildenafil + Pulmonary rehabilitation Programme – Sildenafil 20mg TDS plus a pulmonary rehabilitation programme starting a week later.PDE inhibitors prevent the hydrolysis of cGMP,which has vasodilatory and antiproliferative effects on the pulmonary vasculature that cause the blood vessels to relax.

2. Tadalafil-10mg/day [59].

Statins

1. Atorvastatin – 40mg/day[59]. Treatment with atorvastatin for 9 weeks resulted in attenuation of pH, pulmonary vascular remodeling and RV hypertrophy. Mechanistically, therapy significantly decreased the expression of RhoA and ROCK II and inflammatory infiltration in the lung[60].
2. Pravastatin – 40mg/day[59].

Nifedipine

10 mg TDS[59]. It blocks the voltage dependent L-type calcium channels in vascular smooth muscle and myocardial cells. Reduced intracellular calcium reduces peripheral arterial vascular resistance and dilatation of coronary arteries, leading to a reduction in systemic BP and increased myocardial oxygen delivery[61].

Pentoxifylline

400mg TDS Or 200 mg for patients receiving theophylline[59]. With its anti-inflammatory, antifibrotic and hemorheological properties, pentoxifylline has been demonstrated to increase the

filterability of RBCs, decrease the adherence of RBCs to endothelial cells, blood viscosity, platelet aggregation, fibrinogen levels, and act as a vasodilator and improve pulmonary hemodynamics [62].

Bosentan
It is the endothelin receptor antagonist. Used in the dose of 125mg BD[59]. It blocks the action of endothelin, thus causes the vessels to relax and reduces pulmonary BP to heart and improve its function[63].

Nitric oxide
Oxygen and NO pulsed inhalation of 50ml oxygen and 20 parts per million NO[59]. It can modulate vascular injury and interrupt elevation of PVR selectively; however, it can produce cytotoxic oxygen radicals and can exert cytotoxic and antiplatelet effects[64].

Azithromycin
Azithromycin (0.25mg/day) + Simvastatin (20mg/day)[59]. The combination can relieve ventilation disturbance, improve lung function and decrease pulmonary arterial pressure[65].

FOR COR PULMONALE

Long- term oxygen therapy (LTOT)
For atleast 15 hours a day.This have been shown to improve the QOL and survival in patients with severe chronic hypoxia, by reducing pulmonary arteriolar constriction and improving/slowing the progression of Cor Pulmonale[59]. They are usually recommended where P_aO_2 is less than 55mm Hg or S_aO_2 is less than 88%[66].

Diuretics
Oedema associated with Cor Pulmonale can be controlled with diuretic therapy. Furosemide and Bumetadine are frequently used and in the management of associated peipheraloedema[66]. Care must be taken to avoid over diuresis which can impair the function of both ventricles[67].

CONCLUSION:
Cor pulmonale is due to pulmonary hypertension. The pathophysiology of pulmonary hypertension in COPD is more complex. A diagnosis of cor pulmonale in COPD should prompt a search for causes of pulmonary hypertension. The pulmonary hypertension in COPD adversely affects survival and exercise capacity and is associated with an increased risk of severe acute exacerbations. Many agents have been used in an attempt to reverse the elevated PAP and PVR in cor pulmonale. Other than O_2 which improves exercise performance, and survival rate in

hypoxic patients with cor pulmonale, most agents produced only a modest and transient decrease in PAR.

REFERENCES:
1. World Health Organization. Chronic cor pulmonale: report of an Expert Committee [meeting held in Geneva from 10 to 15 October 1960]. World Health Organization; 1961.
2. Fishman AP. Chronic cor pulmonale. American Review of Respiratory Disease. 1976 Oct;114(4):775-94.
3. Weitzenblum E. Chronic cor pulmonale. Heart. 2003 Feb 1;89(2):225-30.
4. Shujaat A, Minkin R, Eden E. Pulmonary hypertension and chronic cor pulmonale in COPD. International journal of chronic obstructive pulmonary disease. 2007 Sep;2(3):273.
5. Wsphassociation.org. 2022 [cited 7 October 2022]. Available from: http://www.wsphassociation.org/wp-content/uploads/2019/04/Primary-Pulmonary-Hypertension-Evian-1998.pdf
6. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. European Respiratory Journal. 2008 Nov 1;32(5):1371-85.
7. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2005 Apr;2(1):20-2.
8. Mohan H. Textbook of pathology. Jaypee Brothers Medical Publishers; 2018 Nov 30.COR PULMONALE:418
9. MacNee W. Right ventricular function in cor pulmonale. Cardiology. 1988;75(Suppl. 1):30-40.
10. Matthay RA, Arroliga AC, Wiedemann HP, Schulman DS, Mahler DA. Right ventricular function at rest and during exercise in chronic obstructive pulmonary disease. Chest. 1992 May 1;101(5):255S-62S.
11. Hales CA. The site and mechanism of oxygen sensing for the pulmonary vessels. Chest. 1985 Oct 1;88(4):235S-40S.
12. Euler UV, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. ActaPhysiologicaScandinavica. 1946 Aug;12(4):301-20.
13. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circulation research. 2006 Sep 29;99(7):675-91.
14. Wilkinson M, Langhorne CA, Heath D, Barer GR, Howard P. A pathophysiological study of 10 cases of hypoxic cor pulmonale. QJM: An

International Journal of Medicine. 1988 Jan 1;66(1):65-85.

15. Magee F, Wright JL, Wiggs BR, Pare PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. Thorax. 1988 Mar 1;43(3):183-9.

16. Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. Lung. 1992 Mar;170(2):109-24.

17. Santos S, Peinado VI, Ramirez J, Melgosa T, Roca J, Rodriguez-Roisin R, Barbera JA. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. European Respiratory Journal. 2002 Apr 1;19(4):632-8.

18. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, Reid LM, Tuder RM. Pathologic assessment of vasculopathies in pulmonary hypertension. Journal of the American College of Cardiology. 2004 Jun 16;43(12S):S25-32.

19. Dinh-Xuan AT, Higenbottam TW, Clelland CA, Pepke-Zaba J, Cremona G, Butt AY, Large SR, Wells FC, Wallwork J. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. New England Journal of Medicine. 1991 May 30;324(22):1539-47.

20. Lee JD, Taraseviciene-Stewart L, Keith R, Geraci MW, Voelkel NF. The expression of prostacyclin synthase is decreased in the small pulmonary arteries from patients with emphysema. Chest. 2005 Dec 1;128(6):575S.

21. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Stewart DJ. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. New England Journal of Medicine. 1993 Jun 17;328(24):1732-9.

22. Spiropoulos K, Trakada G, Nikolaou E, Prodromakis E, Efremidis G, Pouli A, Koniavitou A. Endothelin-1 levels in the pathophysiology of chronic obstructive pulmonary disease and bronchial asthma. Respiratory medicine. 2003 Aug 1;97(8):983-9.

23. Peinado VI, Barberà JA, Abate P, Ramírez J, Roca J, Santos S, Rodriguez-roisin R. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 1999 May 1;159(5):1605-11.

24. Walter RE, Wilk JB, Larson MG, Vasan RS, KeaneyJr JF, Lipinska I, O'Connor GT, Benjamin EJ. Systemic inflammation and COPD: the Framingham heart study. Chest. 2008 Jan 1;133(1):19-25.

25. Chaouat A, Savale L, Chouaid C, Tu L, Sztrymf B, Canuet M, Maitre B, Housset B, Brandt C, Le Corvoisier P, Weitzenblum E. Role for interleukin-6 in COPD-related pulmonary hypertension. Chest. 2009 Sep 1;136(3):678-87.

26. Kwon YS, Chi SY, Shin HJ, Kim EY, Yoon BK, Ban HJ, Oh IJ, Kim KS, Kim YC, Lim SC. Plasma C-reactive protein and endothelin-1 level in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Journal of Korean medical science. 2010 Oct 1;25(10):1487-91.

27. Kwon YS, Chi SY, Shin HJ, Kim EY, Yoon BK, Ban HJ, Oh IJ, Kim KS, Kim YC, Lim SC. Plasma C-reactive protein and endothelin-1 level in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Journal of Korean medical science. 2010 Oct 1;25(10):1487-91.

28. Alessandri C, Basili S, Violi F, Ferroni P, Gazzaniga PP, Cordova C, COBH Group. Hypercoagulability state in patients with chronic obstructive pulmonary disease. Thrombosis and haemostasis. 1994;72(09):343-6.

29. Erelel M, Ece T, Arseven O. The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. Respiratory medicine. 2002 Jul 1;96(7):515-8.

30. Rizkallah J, Man SP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2009 Mar 1;135(3):786-93.

31. Fraisse F, HOLZAPFEL L, COULAND JM, SIMONNEAU G, BEDOCK B, FEISSEL M, HERBECQ P, PORDES R, POUSSEL JF, ROUX L, Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. American journal of respiratory and critical care medicine. 2000 Apr 1;161(4):1109-14.

32. Keller CA, Osterloh J, Espiritu J, Naunheim KS, McDonald JW, Ramos RR. Histopathologic diagnosis made in lung tissue resected from patients with severe emphysema undergoing lung volume reduction surgery. Chest. 1997 Apr 1;111(4):941-7.

33. Nakamura A, Kasamatsu N, Hashizume I, Shirai T, Hanzawa S, Momiki S, Sasaki K, Kinoshita M, Okada O, Tatsumi K, Kuriyama T. Effects of

hemoglobin on pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic emphysema. Respiration. 2000;67(5):502-6.

34. Deem S, Swenson ER, Alberts MK, Hedges RG, Bishop MJ. Red-blood-cell augmentation of hypoxic pulmonary vasoconstriction: hematocrit dependence and the importance of nitric oxide. American journal of respiratory and critical care medicine. 1998 Apr 1;157(4):1181-6.

35. Azarov I, Huang KT, Basu S, Gladwin MT, Hogg N, Kim-Shapiro DB. Nitric oxide scavenging by red blood cells as a function of hematocrit and oxygenation. Journal of Biological Chemistry. 2005 Nov 25;280(47):39024-32.

36. Eddahibi S, Chaouat A, Morrell N, Fadel E, Fuhrman C, Bugnet AS, Dartevelle P, Housset B, Hamon M, Weitzenblum E, Adnot S. Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. Circulation. 2003 Oct 14;108(15):1839-44.

37. King SJ, Booyse FM, Lin PH, Traylor MA, Narkates AJ, Oparil SU. Hypoxia stimulates endothelial cell angiotensin-converting enzyme antigen synthesis. American Journal of Physiology-Cell Physiology. 1989 Jun 1;256(6):C1231-8.

38. Kanazawa H, Okamoto T, Hirata K, Yoshikawa J. Deletion polymorphisms in the angiotensin converting enzyme gene are associated with pulmonary hypertension evoked by exercise challenge in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2000 Oct 1;162(4):1235-8.

39. Tschernko EM, Gruber EM, Jaksch P, Jandrasits O, Jantsch U, Brack T, Lahrmann H, Klepetko W, Wanke T. Ventilatory mechanics and gas exchange during exercise before and after lung volume reduction surgery. American journal of respiratory and critical care medicine. 1998 Nov 1;158(5):1424-31.

40. Wright JL, Lawson L, Paré PD, Hooper RO, Peretz DI, Nelems JB, Schulzer M, Hogg JC. The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease: the effect of oxygen and exercise. American Review of Respiratory Disease. 1983 Oct;128(4):702-7.

41. Butler J, Schrijen F, Henriquez A, Pow JM, Albert RK. Cause of the Raised Wedge Pressure on Exercise in Chronic Obstructive Pulmonary Disease1, 2. Am Rev Respir Dis. 1988;138:350-4.

42. Richens JM, Howard P. Oedema in corpulmonale. Clinical science (London, England: 1979). 1982 Mar 1;62(3):255-9.

43. Oswald-Mammosser M, Oswald T, Nyankiye E, Dickele MC, Grange D, Weitzenblum E. Non-invasive diagnosis of pulmonary hypertension in chronic obstructive pulmonary disease. Comparison of ECG, radiological measurements, echocardiography and myocardial scintigraphy. European journal of respiratory diseases. 1987 Nov 1;71(5):419-29.

44. Matthay RA, Berger HJ. Cardiovascular function in cor pulmonale. Clinics in Chest Medicine. 1983 May 1;4(2):269-95.

45. Chetty KG, Brown SE, Light RW. Identification of pulmonary hypertension in chronic obstructive pulmonary disease from routine chest radiographs. American Review of Respiratory Disease. 1982 Aug;126(2):338-41.

46. Restrepo CI, Tapson VF. Pulmonary hypertension and cor pulmonale. Textbook of cardiovascular medicine. 1998;2:647-65.

47. Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. European Respiratory Journal. 1995 Sep 1;8(9):1445-9.

48. Tramarin R, Torbicki A, Marchandise B, Laaban JP, Morpurgo M. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. European heart journal. 1991 Feb 1;12(2):103-11.

49. Foster Jr WL, Pratt PC, Roggli VL, Godwin JD, HalvorsenJr RA, Putman CE. Centrilobular emphysema: CT-pathologic correlation. Radiology. 1986 Apr;159(1):27-32.

50. Katz J, Whang J, Boxt LM, Barst RJ. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. Journal of the American College of Cardiology. 1993 May 1;21(6):1475-81.

51. Abraham AS, Cole RB, Green ID, Hedworth-Whitty RB, Clarke SW, Bishop JM. Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studied by serial observations during recovery. Circulation Research. 1969 Jan;24(1):51-60.

52. Garrison DM, Pendela VS, .Yamamoto K, Burnett Jr JC, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular

hypertrophy. Hypertension. 1996 Dec;28(6):988-94.

53. Memon J. Cor pulmonale. InStatPearls [Internet] 2021 Aug 11. StatPearls Publishing.

54. Nadel JA, Murray JF. Textbook of respiratory medicine. Saunders; 2000.

55. Bratel T, Ljungman S, Runold M, Stenvinkel P. Renal function in hypoxaemic chronic obstructive pulmonary disease: effects of long-term oxygen treatment. Respiratory medicine. 2003 Apr 1;97(4):308-16.

56. Weitzenblum E, Apprill M, Oswald M, Chaouat A, Imbs JL. Pulmonary hemodynamics in patients with chronic obstructive pulmonary disease before and during an episode of peripheral edema. Chest. 1994 May 1;105(5):1377-82.

57. Weitzenblum E. Chronic cor pulmonale. Heart. 2003 Feb 1;89(2):225-30.

58. GRIFFITH GC. Cor pulmonale: its diagnosis and management. Diseases of the Chest. 1956 Mar 1;29(3):258-65.

59. NG115 Managing Pulmonary Hypertension and Cor Pulmonale. NICEGuidance(December2018-lastupdated2019)

60. Wang Q, Guo YZ, Zhang YT, Xue JJ, Chen ZC, Cheng SY, Ou MD, Cheng KL, Zeng WJ. The effects and mechanism of atorvastatin on

61. Kashif M. Khan1; Jayesh B. Patel2; Timothy J. Schaefer.Nifedipine. [Updated 2022 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

62. Mohammad Javad F, Seiyed Mohammad Ali G. Effects of pentoxifylline on oxygenation and exercise tolerance in patients with severe chronic obstructive pulmonary disease.

63. https://phassociation.org/patients/treatments/bosentan/#:~:text=Bosentan%20is%20an%20oral%20medication,slow%20progression%20of%20the%20disease.

64. Sim JY. Nitric oxide and pulmonary hypertension. Korean Journal of Anesthesiology. 2010 Jan 1;58(1):4-14.

65. Wang P, Yang J, Yang Y, Ding Z. Effect of azithromycin in combination with simvastatin in the treatment of chronic obstructive pulmonary disease complicated by pulmonary arterial hypertension. Pakistan Journal of Medical Sciences. 2017 Mar;33(2):260.

66. Authored by Dr Colin Tidy, Reviewed by Dr Hayley Willacy | Cor Pulmonale. Last edited 15 Aug 2022 | Meets Patient's editorial guidelines.

67. Weitzenblum E, Chaouat A. Cor pulmonale. Chronic respiratory disease. 2009 Aug;6(3):177-85.

pulmonary hypertension due to left heart disease. PloS one. 2016 Jul 7;11(7):e0157171.