REVIEW OF LITERATURE

DEFINITION
Chronic cor pulmonale is defined as: "Hypertrophy of the right ventricle resulting from diseases affecting the function and / or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart diseases". 

HISTORICAL BACKGROUND
As a concept, cor pulmonale was introduced over 200 years ago but the exact origin of the term is uncertain. Osler commented in the first edition of his textbook that "hypertrophy of the right ventricle … results from increased resistance in the pulmonary circulation, as in cirrhosis of the lung and emphysema". McGinn and White apparently were the first to use the term "acute cor pulmonale" in the discussion of a case of massive pulmonary thromboembolism in 1935.

CLASSIFICATION OF CHRONIC COR PULMONALE
The diseases that may cause chronic cor pulmonale are listed in table-1, classified into broad etiological groups.

Table 1: Diseases Causing Chronic Cor Pulmonale

1) Diseases primarily affecting air passages of the lung and alveoli
   i) Chronic obstructive lung disease (chronic bronchitis and emphysema)
   ii) Asthma (severe, recurrent or chronic)
   iii) Bronchiectasis (including cystic fibrosis)
   iv) Pulmonary interstitial, fibrosis and granulomatous diseases
       a) Fibrosing alveolitis
       b) Tuberculosis
       c) Pneumoconiosis
       d) Radiation
   v) Pulmonary granulomata and infiltration
       a) Sarcoidosis
       b) Berrylliosis
       c) Eosionophilic granuloma
       d) Scleroderma
       e) Malignant infiltration
       f) Dermatomyositis
2) Diseases primarily affecting the movements of the thoracic cage
   i) Kyphoscoliosis and other thoracic deformities
   ii) Thoracoplasty
   iii) Pleural fibrosis
   iv) Chronic neuromuscular weakness
   v) Obesity with alveolar hypoventilation
   vi) Idiopathic alveolar hypoventilation

3) Diseases primarily affecting pulmonary vasculature
   i) Primarily affections on the arterial wall
      a) Primary pulmonary hypertension
      b) Polyarteritis nodosa
      c) Other arteritis
   ii) Thrombotic disorders
      a) Primary pulmonary thrombosis
      b) Sickle cell anaemia
   iii) Embolism
      a) Embolism from thrombosis outside the lungs
      b) Schistosomiasis
      c) Malignant embolism
      d) Other embolism
   iv) Pressure on main pulmonary arteries and veins by mediastinal tumors, aneurysm, granuloma or fibrosis.  

DEFINITION OF ACUTE COR PULMONALE

Acute cor pulmonale is defined as right heart strain or overload secondary to acute pulmonary hypertension often due to massive pulmonary embolism. Most common cause of acute cor pulmonale is pulmonary thromboembolism.

Definition and Diagnosis of Pulmonary Diseases with Special Reference to Chronic Bronchitis and Emphysema.

Most common cause of chronic cor pulmonale is COPD (emphysema, chronic obstructive bronchitis). Badham and Laennec made classical descriptions of chronic bronchitis and emphysema in the early nineteenth century in Western Europe respectively. A British medical text book of the 1860s describes the clinically familiar picture of chronic bronchitis advancing via repeated bronchial
infection to end in oedematous heart failure, causing more than 5% of all deaths in middle and old age; the condition was commonest among the poor and was attributed to bad living conditions. The term chronic obstructive pulmonary disease (COPD) was coined as recently as 1964 and has been widely accepted since then.\(^5\)

**Definition of generalised air flow obstruction**

The original description of COPD emphasized the obstruction to air flow especially on expiration, its large irreversible component and the tendency to progress. Limitation of airflow can result from several pathophysiologic mechanisms.

**Definition of Emphysema**

Emphysema is a condition of lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole, with destructive changes in their walls.\(^4\)

**Definition of Chronic Bronchitis**

Chronic bronchitis is a chronic or recurrent increase above the normal in the volume of bronchial mucous secretion, sufficient to cause expectoration when this is not due to localised broncho-pulmonary disease. The words chronic or recurrent may be further defined as present on most days during at least three months in each of two successive years.\(^4\)

**Pathophysiology of chronic obstructive airway disease**

Limitation of airflow can result from several pathophysiologic mechanisms. Contraction of airway smooth muscle can narrow airways and obstruct airflow. This mechanism is likely to play an important role in asthma and may also contribute to airflow obstruction in other forms of COPD. Narrowing of airways can also be affected by inflammation, oedema or peribronchial fibrosis that can both distort and narrow the airways. Smoking causes these changes probably via elastase and oxidative mechanism, but details are complex.

In COPD right ventricular hypertrophy increases progressively. The main pulmonary arteries are enlarged. The muscles of pulmonary arteries show prominent fibrosis and elastic changes that continues into the arterioles. The small vessels and capillaries are distorted or disappear in region of lung hyperinflation.

**Risk Factors**

**Smoking**
Cigarette smoke plays a prominent role and is undoubtedly the major risk factor for the development of emphysema and chronic bronchitis. It is likely that tobacco smoke can contribute to the development of COPD through several related mechanisms. For example many of the more than 4000 components of cigarette smoke are active oxidants. These species can oxidize methionyl residue at the active side of on alpha protease inhibitor, resulting in an acquired form of protease inhibitor function. Components of smoke can also activate complement system and inflammatory cells and may also inhibit lung repair mechanisms.

Outdoor and Indoor Pollution
In the developed countries, the prevalence of tobacco smoking is declining backed by a strong campaign against smoking through mass media, by educational, legislative and other measures. The prevalence of smoking in the developing countries, on the other hand, has shown an increasing trend. This increase in smoking has been accompanied by increased deaths from COPD. But the mortality rate alone does not tell whole of the story. We must also realise that tremendous morbidity caused by this chronic problem which has serious socio-economic implications. Industrial pollution has also been shown to be one of the important factors predisposing to chronic obstructive pulmonary diseases. In developing countries like Nepal domestic smoke pollution is relatively common particularly in rural areas where people use firewood in poorly ventilated houses for cooking and heating purposes. It is suspected to have an important role in causing chronic lung diseases.3

Hereditary Disease
The classical example of hereditary factor causing chronic obstructive lung disease is the deficiency of alpha 1 antitrypsin. Several genes are associated with alteration in levels of alpha 1 antitrypsin but most common ones associated with emphysema are Z and S genes. It has been postulated that alpha 1 antitrypsin is important for protecting lungs against the action of naturally occurring proteases. The deficiency of alpha 1 antitrypsin has been shown to cause emphysema, which presents itself with dyspnoea on exertion and slight cough at about 40 years of age.3

Clinical Manifestations
The main symptoms of COPD are productive cough, breathlessness of varying severity and wheezing. Breathlessness limits the patients' ability to cope with minor stresses of daily living. During any infection of respiratory tract there is a exacerbation of symptoms leading to frequent emergency hospital admission.
Physical findings

Often there is nicotine staining of the fingers, reflecting many years of heavy cigarette smoking. The skin may be warm and arterial pulses are bounding in the high cardiac output state induced by hypoxia and hypercarbia. The distension of the chest wall due to the airflow obstruction and the ronchi secondary to chronic bronchitis usually make cardiac auscultation difficult. Laboured breathing with use of accessory muscles evidences severe airway obstruction. There may be a characteristics jerky tremor and mental confusion. Cyanosis is prominent in cases with polycythemia. The onset of right ventricular failure is reflected by an increase of jugular venous pressure, the development of large v wave. A right sided protodiastolic gallop (S3) and systolic murmur of tricuspid regurgitation may be audible.

Laboratory Examination

Haematological examinations - reveal raised haemoglobin and the haematocrit.

Pulmonary function tests - Show marked air flow obstruction with increased residual volume and total lung capacity, decreased forced vital capacity (FVC) and markedly decreased expiratory flow rates. In advanced form of the disease FEV1 is less than 1 litre.

Chest Roentgenogram - may shows characteristic changes of emphysema such as hyperlucent lungs, bullae, and increased anterior posterior diameter and flattened diaphragm. An increase in the retrosternal space seen in a lateral radiograph. In some cases increased broncho-vascular markings occur, suggestive of thickened or inflamed airways. The central pulmonary arteries are large but small vessels are narrowed and disappear at the periphery particularly in regions of the lungs that are markedly emphysematous.

The electrocardiography - is relatively insensitive in demonstrating right heart enlargement because the enlarged lungs are poor electrical conductors and the inspiratory position of the chest is associated with vertically positioned heart.

Arterial blood gas study - at rest can be normal when disease is mild, in its severe form show decreased PaO2 (less than 60 mmHg), increased PaCO2 (more than 50mm Hg) and decreased pH.
Echocardiographic imaging - is often difficult because of the air in the distended lungs but it usually reveals an increased cross section of right ventricular cavity and abnormal thickening of the right ventricular wall, in relation to the left.

Right Heart catheterization - can be carried out at the bedside with balloon tipped, flow directed multilumen catheter. It is useful in assessing the severity of the pulmonary hypertension and its response to respiring oxygen as well as left ventricular functions. Pulmonary artery pressure is typically in the range of 40 to 50 mm Hg in-patients with moderate to severe chronic airway obstruction.

Restrictive Lung Disease
Pulmonary parenchymal disease, especially when associated with tissue fibrosis and secondary vascular changes can eventually lead to severe pulmonary hypertension although significant cor pulmonale usually occurs very late. There is very wide range of causes of restrictive lung disease, some like cryptogenic fibrosing alveolitis, sarcoidosis and exposure to inorganic dusts e.g. asbestosis, silicosis is common. Despite the different causes and pathological processes involved, many restrictive lung diseases give rise to similar symptoms, physical signs, radiological changes and disturbances of pulmonary function. Sickle cell disease, from SS or SC haemoglobinopathies can cause cor pulmonale after multiple episodes of pulmonary infarction from pulmonary sickling or thromboembolism. Venoocclusive disease is a rare disease of veins present with pulmonary hypertension.

Disorders of the Neuromuscular Apparatus and Chest Wall -
Common congenital or acquired abnormalities that distort the thoracic cage are kyphoscoliosis, pectus excavatum, pectus carinatum and ankylosing spondylitis. But only kyphoscoliosis is associated with cor pulmonale. These structural abnormalities of the thorax cause repositioning dysfunction, dysfunction of the respiratory muscles, compression of the lung pulmonary vasculature and abnormal gaseous changes.

Weakness of the respiratory muscles can be caused by either generalised muscle diseases such as myopathic infiltrating diseases or muscular dystrophies or more commonly such neurological disorders as a cord lesion or amyotrophic lateral sclerosis, myasthenia gravis, poliomyelitis or Guillain Barre syndrome. These diseases result in generalised alveolar hypoventilation. Chronic cor pulmonale usually develops in response to the hypoxic and hypercapnic stimuli.
**Sleep Apnoea Syndromes**

These are classified into three general groups:

1. Central apnoea, in which, airflow stops in conjunction with cessation of all respiratory muscle effort.
2. Obstructive apnoea, in which upper airway obstruction causes cessation of airflow despite continuing efforts of the respiratory muscles.
3. Mixed apnoea, in which air flow obstruction and respiratory effort both stops initially in the episodes followed first by a resumption of unsuccessful respiratory effort.

The upper airway obstruction in patients with sleep disorder breathing may be due to a combination of such factors is discoordination and relaxation of buccal and pharyngeal muscles, collapse in the walls of the pharynx and backward moment of the tongue due to inactivity of the genioglossus muscle and anatomical factors such as enlarged tonsils and adenoids or narrowing due to marked obesity.

**Chronic cor Pulmonale Secondary to Vascular Disease**

The essential anatomic changes in vascular disease is widespread narrowing or occlusion of pulmonary blood vessels, and the essential physiological change is the consequent increase in pulmonary vascular resistance, leading directly to a continuous increase in the work of the right heart. Primary pulmonary hypertension and recurrent pulmonary thromboembolisms are the common examples among the pulmonary vascular diseases.

**Thrombo-embolism of the pulmonary arteries**

This usually originates in peripheral venous thrombosis. The clinical course is variable. Some cases developing within a few days or weeks (acute cor pulmonale). Whereas chronic cases with recurrent thrombo embolism progress gradually for years. The symptomatology also varies and depends largely upon the presence and size of associated pulmonary infraction. In the final stages cor pulmonale become severe with terminal intractable heart failure. The pulmonary artery pressure is very high and the cardiac output is reduced.

**Multiple embolisation of the lungs by neoplastic cells.**

This arises from a tumour elsewhere and is characterised chiefly by the rapid course of disease. There is a rapidly progressive development of cor pulmonale.
**Primary pulmonary hypertension**

This is considered to be an example of a primary lesion of the pulmonary arterial wall and here little or no parenchymal involvement. There is pathogenic progression from increased pulmonary vasculature resistance resulting from gradual obliteration of the pulmonary vascular bed to pulmonary hypertension and right ventricular over load. Clinically the disease is more often seen in young women than men.

**Pulmonary vascular lesions occurring in situ, secondary to generalized systemic diseases.**

In such diseases as polyarterities or systemic lupus erythematosus, involvement of pulmonary vascular bed may be such as to cause some right ventricular hypertrophy but this is not usually serious part of disease. The thrombosis in situ in the pulmonary vessels in sickle cell anaemia, which may induce cor pulmonale, is usually a late and terminal event.

**Symptomatology and Physical Signs**

The disease is generally symptomless for several months or years. Syncope and oppressive dyspnea on exertion occur later on when the right ventricle fails to increase its output on effort owing to the increased vascular resistance. Anginal pain is rare and haemoptysis is not a common symptom. Cyanosis is absent in uncomplicated cases if it occurs it is peripheral type. Patients in congestive cardiac failure may show central cyanosis. Cardiac arrhythmias are rare and blood pressure is on the lower side of the normal.

A systolic thrust over the lower part of the sternum or to the left of it or in the epigastrium is frequently felt; sometimes a diastolic shock and systolic thrill may be felt over the pulmonary area. On auscultation a loud second sound in the pulmonary area with a pulmonary systolic ejection click suggest pulmonary hypertension.

Radiological findings - dilatation of the pulmonary conus, the pulmonary artery and its branches will be seen. In advanced cases they may reach a size larger that met with in other types. Enlargement of the right ventricle may be seen. The lungs show a clear periphery with prominent hilar shadows.

Electrocardiographic findings - The ECG may be normal in the early stages, later on evidences of right ventricular hypertrophy appear. In advanced cases the ECG changes are extreme.
PATHOLOGY AND INCIDENCE OF CHRONIC COR PULMONALE

Chronic cor pulmonale may be secondary to many diseases and features of one or more these will be present. Marked pulmonary pathology may be seen in diseases of the parenchyma and airways but where the problems are those of the thoracic cage of neuromuscular or respiratory control mechanism, lung damage may be slight.\textsuperscript{7}

Approximately 20 percent of hospital admissions for heart failure are caused by right heart failure associated with chronic cor pulmonale.\textsuperscript{8} More than half of the patients with chronic obstructive lung diseases have cor pulmonale and this condition constitutes between 5 and 10 percent of all adult heart diseases in the United States.\textsuperscript{8} Cor pulmonale constitutes higher percentages of all form heart diseases in countries where the obstructive lung disease is higher such as United Kingdom.\textsuperscript{8}

A high prevalence of chronic cor pulmonale has been reported from many developing countries usually ranking fourth in the order of frequency after rheumatic heart disease, hypertension and coronary artery disease. Hospital statistics in different countries reveal that in India 5.30 percent of the cardiac cases have chronic cor pulmonale, whereas it is 6 percent in Hongkong, 3 percent in Philippines, 8 percent Iran, 4 percent in Malaysia and 11 percent in Iraq.\textsuperscript{9}

In Nepal hospital admissions of chronic cor pulmonale was seen to be leading cardiac admission forming as much as 46 percentage of the cases.\textsuperscript{9} Hospital statistics however are known to have limitations assessing the disease prevalence.

A house to house survey for prevalence of chronic cor pulmonale in a hilly region of Nepal revealed it to be about 1 percent.\textsuperscript{9}

**The Right Ventricle**

Right ventricular hypertrophy is the hallmark of chronic cor pulmonale but it's extent varies greatly. Increases in weight range slightly above normal (60 g) to as high as 200 g and the right ventricular wall thickness may become greater than 0.5 cm.\textsuperscript{7}

**The Left Heart**

The left ventricle becomes slightly hypertrophied in patients with cor pulmonale even where no valvular or systemic vascular disease. This may be a response to hypoxia and or erythorcytosis.\textsuperscript{7}
Chronic left ventricular filling impairment is present despite a normal systolic pressure, due to septal leftward shift. In fact, chronic right ventricular pressure overload distorts early diastolic left ventricular geometry delaying left ventricular pulse, and the functional diastolic impairment of the left ventricle is closely correlated to pulmonary hypertension.  

**The Carotid body**

The carotid body is enlarged due to an increased number of chief cells. The clinical significance of this is not known.  

**DISTURBANCES IN THE HAEMODYNAMIC OF THE PULMONARY CIRCULATIONS**

The pulmonary vascular resistance to which pulmonary blood pressure and blood flow are related determines the work of right ventricle. The hypertrophy of the right ventricle found in chronic cor pulmonale arises from increased work due to changes in the haemodynamics of pulmonary circulation in disease.

The response of the right ventricle to pulmonary hypertension depends on the acuteness and severity of the pressure load. Chronic cor pulmonale however is associated with more slowly evolving and slowly progressing hypertension.  

The severity of the hypertension, the rapidity with which it becomes severe and the possible eventual onset of right ventricular failure are influenced by following factors:

1) Alterations in ventricular function causing alveolar pressure changes with effects on chamber function.
2) Alterations in gas exchange with more or less severe hypoxaemia, hypercapnia and acidosis.
3) Alterations in volume load as influenced by exercise, heart rate, polycythaemia, renal retention of salt and water associated with cor pulmonale

The myocardium is unable to function at the high-pressure load and the right ventricle dilates and fails. Right ventricular failure may occur relatively early in some patients with chronic bronchitis and emphysema because of sustained hypoxia and hypercarbia.

Significant pulmonary hypertension and right ventricular hypertrophy can occur in normal persons living at extreme altitude with no evidence of heart failure.
CLINICAL RECOGNITION OF CHRONIC COR PULMONALE

Clinical manifestations of chronic cor pulmonale are often obscured by signs and symptoms of underlying disease and are therefore, closely related to pulmonary disease. It is necessary to recognise type and severity of lung disease and look for cor pulmonale.

There is no history specific for cor pulmonale. Episode of leg oedema, atypical chest pain, dyspnoea on exertion, peripheral or central cyanosis and excessive day time somnolence are usual presentations of chronic cor pulmonale. Chest pain may be due to strain or distortion of the chest wall or may be related to right ventricular ischemia. Cough and easy fatigability are common in some patients. Nocturnal hypoventilation and sleep apnoea may present with personality changes.

Heart failure occurs insidiously causing further impairment of the lung function but frequently is misinterpreted as worsening of the underlying disease. Diagnosis is often not made until significant right ventricular hypertrophy or right ventricular failure is present, but chronic cor pulmonale should be considered in any patient with pulmonary hypertension and particularly with disorders causing chronic hypoxaemia.

The cardiac signs are often concealed by distension of the overlying lung. But epigastric systolic thrust may be present. This is indeed the only physical sign directly related to right ventricular hypertrophy. Usually its exact position varies; being sometimes to the left of sternum, sometimes over sternum itself and sometimes in the epigastrium. Other physical signs including loud pulmonary second sound, a gallop rhythm and prominent jugular venous pulsation are related either to the severity of the pulmonary hypertension or to right heart failure.\textsuperscript{13}

With very high pulmonary artery pressure characteristic systolic murmur of tricuspid regurgitation can be heard. In overt right ventricular failure, cardiac enlargement, distended neck veins, hepatomegaly, hepatic pulsation, ascitis and peripheral oedema are present.\textsuperscript{14}

RADIOLOGICAL FINDINGS

There may be no observable cardiac abnormalities in the chest radiography. X-ray pictures are dominated by the primary pathology particularly emphysema with diaphragmatic descent.
There may be enlargement in the transverse diameter of the heart in the posterior anterior view with an alteration in the contour of pulmonary conus with filling of the normal concavity or actual convexity. Dilatation of the stem and main pulmonary artery is also seen. 3

**ELECTROCARDIOGRAPHIC FINDINGS IN CHRONIC COR PULMONALE**

There may be no alterations in the electrocardiogram in case of chronic cor pulmonale in spite of the presence of right ventricular hypertrophy at autopsy 4.

The complexity of the electrocardiographic changes of chronic cor pulmonale rests, in part at least, with the fact that the electrical potentials may be altered by structural changes outside the heart as well as by those within the right ventricle. Electrical potentials from the right ventricle may be modified by:

1) Changes in the anatomic orientation of the right ventricle.
2) Changes in the right ventricular myocardium.
3) Changes in the time course of ventricular depolarization15.

**Electrocardiographic Criteria of Diagnosis**

q R pattern with delayed R wave in V1 is highly suggestive of right ventricular hypertrophy but is not commonly seen in chronic cor pulmonale.

In the absence of qR pattern a combination of at least of two of following changes must be present:

1) Alteration in the ratio R/S in the left chest lead with R/S less than 1 in V5.
2) Predominant S wave in standard lead I.
3) Presence of an incomplete right bundle branch block with QRS less than 0.12 second.

Others:

1) P-pulmonale characterised by P wave in lead II of 2.5 mm or more in height (may be present but is not diagnostic).
2) Right axis deviation of more than 110 degree may be found associated with inversion of T wave in V1 to V4 or II, III leads.

**ECG CRITERIA OF COR PULMONALE WITHOUT OBSTRUCTIVE DISEASE OF THE AIRWAYS**

1) Right axis deviation with a mean QRS axis to the right of +110.
2) R/S amplitude ratio V1 more than 1.
3) R/S amplitude ratio V6 less than 1.
4) Clock wise rotation of the electrical axis.
5) P pulmonale pattern.
6) $S_1$, $Q_3$ or $S_1$, $S_2$, $S_3$ pattern.

**ECG CHANGES IN CHRONIC COR PULMONALE WITH OBSTRUCTIVE DISEASE OF THE AIRWAYS**

1) Isoelectric P wave in lead I or right axis deviation of the P vector.
2) P pulmonale pattern
3) Tendency of right axis deviation of the QRS.
4) R/S amplitude ratio V6 less than 1.
5) Low voltage QRS.
6) $S_1$, $Q_3$, or $S_1$, $S_2$, $S_3$ pattern.
7) R/S amplitude ratio in V1 more than 1.
8) Incomplete right bundle branch block
9) Marked clockwise rotation of the electrical axis.
10) Occasional large Q wave or QS in the inferior or mid precordial leads, suggesting healed myocardial infraction.

**PULMONARY FUNCTION TEST**

In 1946 Hutchinson described a water spirometer very similar to the one used today and used it to analyse his data on measurement of vital capacity in more than 2000 people. Spirometer basically consists of a device that measures the volume of air inspired and expired and record the time over which the volume changes occurs.

Various simple methods are available for estimating impairment of ventilatory function. The most widely used method that is both valid and if correctly performed, relatively free from subject and observer variation is the measurement of the maximum volume of air the subject can exhale after a full inspiration. Two such volumes are:

1) Forcibly expired volume during the first second of expiration $FEV_1$, and
2) Volume expired to full expiration (VC).

A spirometric tracing of minute volume, forced expiratory and inspiratory vital capacities and of maximum voluntary ventilation can provide additional valuable information.

**Patterns of abnormal ventilatory capacity**

Two classical patterns of ventilatory defects seen are obstructive and restrictive type of defects. Pulmonary function tests reveal following pattern of volume and the ratio changes:
### ARTERIAL BLOOD GAS ANALYSIS

Hypoxaemia is defined physiologically as arterial oxygen tension (PaO$_2$) decreased below normal limits. Hypercapnia and hypocapnia are defined respectively as increase and decrease in arterial carbon dioxide tension (PaCO$_2$) beyond normal limits.\(^4\)

Modern automatic analysers give a rapid direct readout of PaO$_2$, PaCO$_2$ and hydrogen ion concentration in arterial blood often supplemented by derived variables (such as O$_2$ saturation and bicarbonate concentration). This is of value in assessment of hypoxaemia or acid base balance. Such measurements are particular value in the management and prediction of prognosis in respiratory failure, exacerbation of chronic cor pulmonale and acute respiratory distress syndrome\(^{26,27}\).

Pulse oximetry - over the past several years an alternative method for assessing oxygenation and has become readily available in many clinical settings. The pulse oxymeter measures oxygen saturation rather than PO$_2$ using a probe usually clipped over a patient's finger\(^{27}\).

The normal ranges of PaO$_2$, PaCO$_2$, HCO$_3$ and pH are as follows\(^{28,21}\):

<table>
<thead>
<tr>
<th>Test</th>
<th>Obstructive</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>↓ ↓</td>
<td>↓</td>
</tr>
<tr>
<td>VC</td>
<td>↓ or normal</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>FEV1 / VC</td>
<td>↓</td>
<td>Normal or ↑</td>
</tr>
</tbody>
</table>

PaO$_2$ 80 - 100 mm Hg (12-15 kPa)
PaCO$_2$ 35 - 45 mm Hg (4.4-6.1kPa)
HCO$_3$ 22 - 28 meq/L (21-27.5mmol/L)
PH 7.35 - 7.45
O$_2$ Saturation %age >97%

In chronic cor pulmonale PaO$_2$ ranges from 45 - 53 mm Hg (6 to 7 KPA) or lower. Arterial carbon dioxide PaCO$_2$ is more variable - 60 - 68 mm Hg (8 to 9 KPA) or higher. Haemotocrit is frequently raised above 55%.\(^{29,30}\)

### ECHOCARDIOGRAPHY
Echocardiogram of the right ventricle is less informative than that of the left side of the heart. Doppler echocardiography has improved the assessment of pulmonary artery pressure. The principle technique for determining pulmonary artery pressure involves the use of the tricuspid regurgitant jet and the Bernoulli equation. The formula of calculation being $P=4V^2$ (P= Systolic Pulmonary Artery Pressure and V= Velocity of blood flow). By determining the right ventricular systolic pressure and ruling out the existence of any obstruction in the right ventricular outflow tract, one can determine pulmonary artery systolic pressure. The technique is probably the most accurate for quantitating pulmonary artery pressure.

Tricuspid regurgitation occurs in patients with COPD. By augmenting the signal with an intravenous infusion of saline, the quality of the signal to detect tricuspid regurgitation using continuous wave Doppler echocardiography can be improved.

Pulsed wave Doppler echocardiography was even more sensitive for detecting tricuspid insufficiency in one study. Systolic pulmonary artery pressure could be measured in 91% of patients with COPD. Moreover, the pulse wave Doppler echocardiography technique can be used to assess changes in pulmonary artery pressure during exercise. Cardiac catheterization results have been compared with those using echocardiography measurements of pulmonary artery pressure and showed good correlation.

The difficulty in differentiating the right ventricular wall from its surrounding structures limits the use of echocardiography for detecting right ventricular hypertrophy. Echocardiography measured right ventricular wall thickness has correlated poorly with right ventricular weight determined at autopsy.

Putnik M, Povazon D, Vindis Jesic M., in 1998 concluded that echocardiography had better sensitivity than ECG in diagnosing chronic heart disease and both methods are non-invasive, easily applicable and have an important role in examining cardiac changes in patients with COPD.

Steiniger L et al in 1993, reported that echocardiography is a reliable method of assessing right ventricular function. Doppler echocardiography is most useful with a specificity and sensitivity of about 80%.

Alvin Cacho, Ravi Prakash et al in 1993 in their study 'Two dimensional echocardiography using a subcostal approach in patients with COPD' concluded that two-dimensional echocardiography is
able to quantify the morphologic changes of the right heart in the patients with COPD and can be of practical use in the assessment of pulmonary hypertension\textsuperscript{47}.

Schmidt H; Kirsten D; Piolesch W in 1987 observed that the echocardiography criteria of right ventricular hypertrophy and dilatation of right sided cavities of the heart had sensitivity of 0.809 and specificity of 0.75\textsuperscript{48}.

\textbf{RIGHT SIDED HEART CATHETERIZATION}

The most accurate method to define the altered state of the pulmonary circulation in cor pulmonale is cardiac catheterization, which permits measurement of blood flow and pressures. Cardiac catheterization is needed however in only few patients for confirmation of diagnosis\textsuperscript{4}.

In COPD, pulmonary arterial pressure is related to the level of the hypoxaemia and usually will decrease by oxygen administration\textsuperscript{49, 50, 10}.

Pulmonary artery hypertension is usually considered to be present when the mean pressure in pulmonary artery exceeds 25 mm Hg at rest\textsuperscript{4}.

\textbf{REGARDING DIAGNOSIS OF CHRONIC COR PULMONALE}

The Clinical, radiological, electrocardiographic and haemodynamic findings (Doppler or Two-dimensional echocardiography and right heart catheterization) should be considered together because the diagnosis of right ventricular hypertrophy becomes increasingly probable with increase in the numbers and severity of abnormalities demonstrated.\textsuperscript{4} For the final confirmation of the diagnosis these findings need to be correlated with autopsy findings.

\textbf{THE DIFFERENTIAL DIAGNOSIS OF CHRONIC COR PULMONALE}

In many patients of right heart failure, hypoxia and respiratory disease coexist. The question then arises: Is this a cor pulmonale? To answer this may be difficult because respiratory diseases are common and non-respiratory causes of pulmonary hypertension also eventually lead to secondary hypoxia\textsuperscript{7}.

The differential diagnosis consists of:

1) Pulmonary hypertension from unrecognised left heart failure or pulmonary veno-occlusive disease.
2) Pulmonary arterial occlusive disease from emboli.
3) Primary pulmonary hypertension.

The diagnosis of cor pulmonale requires demonstration: that respiratory disease is sufficiently severe to generate the necessary degree of hypoxia; and that no other cause of pulmonary hypertension is present. In the first instance, the severity of respiratory disease is evaluated clinically but detailed pulmonary function tests and blood gas measurements will also be needed.

In the elimination of cardiac causes of pulmonary hypertension, left heart failure can be identified by clinical examination but mitral stenosis and shunts may present problems that require echocardiography and cardiac catheterization for their solution. A large pulmonary emboli may frequently be identified by a clinical history aided by ventilation perfusion scanning and if necessary pulmonary angiography.

**NATURAL HISTORY AND PROGNOSIS**

Prognosis depends on control of the underlying lung disease and control of pulmonary hypertension. Patient with COPD has hypoxic pulmonary hypertension that is to a great extent reversible and right ventricular failure can be improved with appropriate therapy. Even with repeated episode of right ventricular failure some may survive for long time\(^{51,52}\). The pink puffers tend to live longer than the blue bloaters\(^{53}\). Cigarette smoking may determine the severity of secondary polycythaemia in patients with hypoxia and prevents its correction by long term oxygen therapy\(^{24}\).

Once right ventricular failure occurs prognosis is usually very poor. Even though right ventricular failure occurs most often in the terminal phase of illness, there is report of 7 - 8 years survival after the diagnosis of cor pulmonale.

The quality of life in COPD with the chronic cor pulmonale is related to the severity of hypoxaemia but relationship is only detectable when using a disease specific health measure\(^{54,55}\). The outlook for longevity is much better in patients with chronic bronchitis and emphysema in whom blood gases can be maintained at a near normal levels\(^{56,57}\).

Even with modern techniques for diagnosis and management, the prognosis for the underlying disease has not been greatly improved. The prognosis for cor pulmonale however, is much better because of newer technique. Early recognition of the problem and better understanding of hypoxia help to take measures to prevent fast developing pulmonary hypertension\(^{5,58,59}\).
TREATMENT

Principles of treatment of pulmonary diseases that may cause chronic cor pulmonale

The condition most commonly responsible for cor pulmonale is chronic obstructive airway disease and episode of frank heart failure commonly first appears during the infective exacerbation. Many management options are available for the clinician to relieve symptoms and improve quality of life in patients in all stages of symptomatic COPD. Only oxygen therapy has been the subject of randomised controlled trial which showed it to increase survival and improve the quality of life\textsuperscript{7,60}.

Avoidance of Bronchial irritants

All patients with chronic bronchitis should be advised to stop smoking, to avoid exposure to smokes and to take special precautions during fog. A change of occupation is indicated if there is clear evidence of that some particular dust or fume to which a patients is exposed exacerbates his symptoms, and if patient is employed out of doors in smoky environments\textsuperscript{4}.

Treatment of Infection

Exacerbations of bronchial infection are nearly always the precipitating cause of cardiac failure in these patients\textsuperscript{4}. The most common pathogenic bacteria found are Streptococcus pneumoniae Haemophilus influenzae, and Moraxella catarrhalis. Although still somewhat controversial antibiotics are frequently used in the treatment of the COPD exacerbation and have been shown to shorten the course of acute exacerbation \textsuperscript{61,62}. Since most infectious exacerbation are viral in origin it is not surprising that in typical cases antibiotics are of dubious benefit. Examination of sputum for Gram's Stain and sputum culture and sensitivity may be of help in determining the need for antibiotics. Suitable agents include Ampicillin, Amoxycillin, Cephalosporins, Quinolones, Tetracyclines or Trymethoprim/Sulphamethoxazole. In the event that resistant organisms are likely, the combination of amoxycillin and clavulanic acid or a macrolide such as azithromycin or clarithromycin may be appropriate. In some countries it is common practice to give continuos antibiotic therapy during the winter months in order to prevent mucopurulent relapses. Usual coarse of antibiotic given is 7-10 days.

Finally, Amantadine or Rimantadine therapy should be considered in unimmunized COPD patients with suspected acute influenza\textsuperscript{63}. 

**Bronchoactive Drugs**

Bronchodilators are administrated to reverse the bronchoconstriction (bronchospasm). These drugs can be given by inhaled, oral, subcutaneous and intravenous routes. However the inhaled routes is preferred due to the direct effects on the lung with relatively less systemic effect $^{64,65}$.

The most common mistakes in bronchodilator management include inadequate education regarding medication dosing (too little or too much), inadequate monitoring of patient's response to treatment and a lack of detailed pre-treatment evaluation.

**Anticholinergics**

Anticholinergic agents are now an integral part of therapy and are considered to be first line agents by many. Anticholinergic such as atropine and Ipratropium bromide have been reported to produced greater bronchodilation then $\beta_2$ agonist at conventional dosages$^{66}$. In addition Ipratropium bromide has been shown to reduce the sputum volume without altering sputum viscosity. The recommended dosing for Ipratropium is two puffs four times daily or higher dosages of three to six puffs four times daily with a spacer $^7$.

**Sympathomimetics**

Sympathomimetics have been the mainstay of the COPD management for years although their role as a first line agent has been challenged by Ipratropium bromide$^{68,69}$. Selective $\beta_2$ stimulating agent such as salbutamol, albuterol, terbutaline and metaproterenolol can be given both orally and by aerosol. Fewer cardiac side effects are experienced with isopreterenolol. Orally and parentally administered $\beta_2$ agonists are effective but are associated with greater tremulousness and cardiovascular side effects than those resulting from inhaled agents.

Potential for inducing hypokalaemia with higher dosages of $\beta_2$ agonist must also be recognised and monitored in patients at risk. In general $\beta_2$ adrenoreceptors agonist have a rapid time of onset and are preferred for the treatment of acute bronchospasm.

**Theophylline**

Most commonly used theophylline is methylxanthine derivative (Aminophylline) which can be given orally or parentally in addition to their bronchodilators. It stimulates respiration, has cardiotonic effect and diuretic properties and may increase diaphragmatic contractility especially in the setting of hypoxaemia or muscle fatigue. Blood level between 10 and 15 mg/l should be maintained. Side
effects such as nervousness, insomnia are frequent even when levels are in therapeutic range. Nausea, vomiting, tachyarrhythmias and seizures are seen mainly when blood levels exceed 20 mg/l.

Evening dosing with long acting theophylline preparation has been shown to reduce overnight falls in FEV1 and improve morning respiratory symptoms in patients using inhaled bronchodilators. Eleven patients treated for average of four months had sustained improvement in right ventricular ejection and also even left ventricular ejection fraction increased slightly.

**COMBINED BRONCHODILATATOR THERAPY**

In many instances, the combination of several bronchodilator agents may provide added effects. The combination of beta two agonists and anticholinergic in the same MDI (Metered dose inhaler) has been shown to have are additive effect, especially when typically recommended lower doses of each agent are used. Theophylline and beta two agonist have also been shown to have additive bronchodilator effects and combination is usually well tolerated.

**GLUCOCORTICOIDs**

These drugs are effective in a proportion of cases of generalised airways obstruction, but it is difficult to forecast which patients are likely to respond. In general those with persistent infection seldom respond, while those with on asthmatic type of history or with marked sputum eosinophilia are most amenable to therapy.

In several trials no more than 20 to 30 percent of COPD patients showed objective benefits when long term steroid was given. A trial of therapeutic corticosteroids for about two weeks should be considered in patients who have continued symptoms or severe airway limitation despite maximal therapy with other agents. Only those patients with significant documented physiological improvement should be considered for long term therapy with a goal of reducing dosages to the lowest possible.

**OTHERS MEASURES**

1) **Vaccines:** Patients with COPD have an increased risk for respiratory tract infections. Infection prophylaxis by vaccination can reduce the incidence and severity of bronchial infections reducing the morbidity and mortality associated with the infections. Although the benefits of the pneumococcal vaccine have been debated, pneumococcal vaccination is currently recommended for all COPD patients. The current pneumococcal vaccine is 23 valent covers more than 80% of
pneumococcal strains and is 60% effective in producing antibodies in immunocompetent patients. Animal vaccine prophylaxis against influenza is also recommended for all patients of COPD with vaccine formulation and potency revised yearly. Both influenza and pneumococcal vaccine are under-utilised. Less than 30% of high-risk patients are immunised for influenza each year and less than 10% of patients receive the pneumococcal vaccines even in developed countries\textsuperscript{78}.

2) Respiratory stimulants - including Doxapram, medroxyprogesterone and acetazolamide have been suggested as a means of increasing ventilation. Unfortunately the stimulating effects of these agents are frequently short lived.

3) Antiproteases and antioxidants- Recognition of alpha antitrypsin deficiency as a cause for the early development of emphysema has led to an increasing awareness of the role of protease/antiprotease oxidant/antioxidant imbalance in the development of COPD\textsuperscript{76}. Even non-specific antioxidants such as vitamin C and E have been proposed as treatment for those diseases.

4) Bronchopulmonary drainage and maintenance of total body hydration have important role in the management of chronic respiratory diseases.
PRINCIPLES OF TREATMENT OF CARDIAC FAILURE IN CHRONIC COR PULMONALE

The development of pulmonary hypertension and chronic cor pulmonale in patients with chronic respiratory diseases (obstructive, restrictive and mixed) indicates a poor prognosis. The primary aetiology for these changes is hypoxaemia, for which lung term oxygen recommended. Various vasodilators have been investigated in an attempt to reduce pulmonary hypertension and its sequelae.

OXYGEN
Survival Benefit

In clinical trials sponsored by United States National Institute of Health (Nocturnal oxygen therapy trial group 1980) and British Medical Research Council 1981 - long term oxygen therapy clearly improved the survival of hypoxaemic patients with COPD79,80.

How oxygen therapy improves survival is not known. Two hypothesis have been proposed:

1) Oxygen relieves pulmonary vasoconstriction decreasing pulmonary vascular resistance and thus enabling the right ventricle to increase stroke volume.

2) Oxygen therapy improves arterial oxygen content providing enhanced oxygen delivery to the heart, brain and other vital organs81,82.

PRESCRIBING CRITERIA OF LONG TERM OXYGEN THERAPY

1) PO\textsubscript{2} less than 55 mm Hg or SaO\textsubscript{2} less than 88% breathing room air.

2) PO\textsubscript{2} less than 59 mm Hg and evidence of at least one of the following: pulmonary hypertension (P wave more than 3 mm in leads II, II aVF) cor pulmonale, dependent oedema, or haematocrit more than 55%.

A system of patient selection proposed by the (United Kingdom) Department of Health suggest that the patient should fall in one of three groups.

1) Cor pulmonale

2) Chronic hypoxic bronchitis and emphysema

3) Hypoxic lung disease requiring paliation.

Arterial oxygen pressure should be less than 55 mm Hg (7.3 KPA), PCO\textsubscript{2} more than 45 mm Hg (6 KPA) and expiratory volume FEV1 less than 1.5 litre to prescribe long term low concentration oxygen therapy.
For long-term oxygen therapy in human, results suggests that $O_2$ must be given in low dose 2 litre/min or low concentration 24%. The $O_2$ must be taken continuously for at least 12-18 hours each day.

**DIURETICS**

The use of diuretics reduces oedema, improves peripheral circulation, allows improved ventricular contractile efficiency by reducing intravascular volume and may also improve gas exchange in the lung if pulmonary extravascular water has increased. Usually powerful diuretics such as Frusemide are used or combined diuretic therapy may be used. An important complication of diuretic therapy may be metabolic alkalosis in the presence of potassium deficiency. This is particularly a problem in chronic obstructive airway disease because the alkalosis may further reduce the $CO_2$ sensitivity of the medullary centre.

**DIGITALIS**

Digitalis therapy should be used only in patients with cor pulmonale and coexistent left ventricular failure. Digoxin is useful in rate control for chronic arterial fibrillation associated with chronic cor pulmonale.

For example Mathur et al evaluated the effect of eight weeks of digoxin therapy on resting right ventricular function in patients with severe COPD. All patients were found to have a reduced right ventricular ejection fraction at the start of the therapy, but only patients with reduced initial left ventricular ejection fraction showed an improvement.

Another study indicated that intravenous digoxin improved diaphragm strength blood flow in patients with COPD who had acute respiratory failure. Therefore, there must be role for digoxin in the management of the acutely decompensated patient.

**VASODILATATORS**

Vasodilator therapy should be considered in patients with COPD only when conventional therapy and oxygen have failed to improve signs of right ventricular failure or pulmonary hypertension because these agents have potentially adverse consequences.

Various vasodilatators have been evaluated in patients with chronic cor pulmonale including nitrates, hydralazine, calcium channel antagonists (nifedipine and verapamil), angiotension converting enzyme inhibitors (captopril and enalapril) and prostaglandin. The results of studies with these...
agents have been equivocal and none of these agents is currently used in routine clinical practice

PHLEBOTOMY
The increased in haematocrit in chronic hypoxia is initially an adaptive response to reduced oxygen saturation. As the haematocrit rises progressively above 50% blood viscosity increases significantly and this increase, together with thrombosis and sludging in the pulmonary circulation, adds to right ventricular strain.

Whether phlebotomy is efficacious in polycythaemic patients with cor pulmonale is controversial. Still some haemodynamics studies have shown that optimal benefit is obtained by reduction of haematocrit above 60% to values in the mid or low fifties and that this should be achieved by exchange transfusion with low molecular weight dextran solutions (Haemaccel). It is not clear that there are any long term benefits and overall phlebotomy should be reserved as adjunctive therapy in acute situations.