Evaluation of Erythropoietin hormone in Chronic Obstructive Pulmonary Disease patients during Exacerbation and after Remission

Thesis
Submitted for fulfillment of Master Degree in Chest Diseases & Tuberculosis

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<td>AECOPD</td>
<td>Acute exacerbation of chronic obstructive pulmonary disease.</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation.</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Is a software package used for statistical analysis.</td>
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<td>BFU-E</td>
<td>Burst-Forming Unit-Erythroid.</td>
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<td>BLVRS</td>
<td>Bronchoscopic Lung Volume Reduction Surgery.</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index.</td>
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<tr>
<td>BODE</td>
<td>Body mass index, obstruction, dyspnea and exercise.</td>
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<td>CAT</td>
<td>COPD assessment test mMRC.</td>
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<tr>
<td>CD 4</td>
<td>Cluster designation antigen 4.</td>
</tr>
<tr>
<td>CD 8</td>
<td>Cluster designation antigen 8.</td>
</tr>
<tr>
<td>CFU-E</td>
<td>Colony-forming unit-erythroid.</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein.</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography.</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease.</td>
</tr>
<tr>
<td>CXCLR 3</td>
<td>CX chemokine ligand receptor 3.</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusion capacity of the lung to carbon monoxide.</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxynucleic Acids.</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Venous Thrombosis.</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram.</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor.</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme linked Immunosorbent Assay.</td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoietine hormone.</td>
</tr>
<tr>
<td>Epo mRNA</td>
<td>Erythropoietin Messenger Ribonuclear Acid.</td>
</tr>
<tr>
<td>EpoR</td>
<td>Erythropoietin receptor.</td>
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<td>ESA</td>
<td>Erythropoiesis-stimulating agents.</td>
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<td>ETS</td>
<td>Environmental tobacco smoke.</td>
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<tr>
<td>FEF25-75%</td>
<td>Forced expiratory flow between 25 to 75% of forced vital capacity.</td>
</tr>
<tr>
<td>FEF50%</td>
<td>Forced expiratory flow at 50% of forced vital capacity.</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in the first second.</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat free mass.</td>
</tr>
<tr>
<td>F-V loop</td>
<td>Flow volume loop.</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity.</td>
</tr>
<tr>
<td>g/dl</td>
<td>gram/ deciliter.</td>
</tr>
<tr>
<td>GATA-2</td>
<td>GATA binding protein 2 a transcription factor.</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease.</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobine.</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematocrit.</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure.</td>
</tr>
<tr>
<td>HIF-1</td>
<td>Hypoxia-inducible transcription factor-1.</td>
</tr>
<tr>
<td>HIF-2</td>
<td>Hypoxia-inducible transcription factor-2.</td>
</tr>
<tr>
<td>HIFs</td>
<td>Hypoxia-inducible transcription factors.</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immune deficiency virus.</td>
</tr>
<tr>
<td>HRCT</td>
<td>High resolution computed tomography.</td>
</tr>
<tr>
<td>HREs</td>
<td>The hypoxia-response elements.</td>
</tr>
<tr>
<td>HRP</td>
<td>Horseradish Peroxidase (HRP) Substrates.</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroid.</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit.</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart diseases.</td>
</tr>
<tr>
<td>IL-1</td>
<td>Interleukin -1.</td>
</tr>
<tr>
<td>IL-4</td>
<td>Interleukin -4.</td>
</tr>
<tr>
<td>IL-5</td>
<td>Interleukin -5.</td>
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<td>Interleukin -6.</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin -8.</td>
</tr>
<tr>
<td>IMV</td>
<td>Invasive Mechanical Ventillation.</td>
</tr>
<tr>
<td>JAK2</td>
<td>Cytoplasmic Janus kinases 2.</td>
</tr>
<tr>
<td>kDa</td>
<td>Killo-Dalton.</td>
</tr>
<tr>
<td>LTB4</td>
<td>Leukotriene B4.</td>
</tr>
<tr>
<td>LTD4</td>
<td>Leukotriene D4.</td>
</tr>
<tr>
<td>LVRS</td>
<td>Lung volume reduction surgery.</td>
</tr>
<tr>
<td>µg</td>
<td>Microgram.</td>
</tr>
<tr>
<td>MDI</td>
<td>Metered dose inhaler.</td>
</tr>
<tr>
<td>mEPHX1</td>
<td>Microsomal epoxide hydrolase 1.</td>
</tr>
<tr>
<td>MMP12</td>
<td>Matrix metalloproteinase 12.</td>
</tr>
<tr>
<td>mU/ml</td>
<td>Milliunit/Milliliter.</td>
</tr>
<tr>
<td>n&amp;%</td>
<td>Number and percentage.</td>
</tr>
<tr>
<td>NESP</td>
<td>Novel erythropoiesis-stimulating protein.</td>
</tr>
<tr>
<td>NPPV</td>
<td>Non-invasive positive pressure ventilation.</td>
</tr>
<tr>
<td>Nrf2</td>
<td>A transcription factor called Nrf2.</td>
</tr>
<tr>
<td>OD</td>
<td>Optical density.</td>
</tr>
<tr>
<td>O-DDD</td>
<td>O2-dependent degradation domains.</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea.</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Partial pressure of carbon dioxide in arterial blood.</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Partial pressure of oxygen in arterial blood.</td>
</tr>
<tr>
<td>PDE4</td>
<td>Phosphodiesterase 4.</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow.</td>
</tr>
<tr>
<td>PHD-2</td>
<td>Prolylhydroxylases-2.</td>
</tr>
<tr>
<td>PHD-3</td>
<td>Prolylhydroxylases-3.</td>
</tr>
<tr>
<td>R</td>
<td>Remission.</td>
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<tr>
<td>RhEpo</td>
<td>Recombinant human erythropoietin.</td>
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<tr>
<td>SaO₂</td>
<td>Oxygen saturation in arterial blood.</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation.</td>
</tr>
<tr>
<td>SGRQ score</td>
<td>St. George's Respiratory Questionnaire.</td>
</tr>
<tr>
<td>SPSSV.11.</td>
<td>Is a software package used for statistical analysis.</td>
</tr>
<tr>
<td>St t test</td>
<td>Student's test.</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Transforming growth factor beta 1.</td>
</tr>
<tr>
<td>TMB</td>
<td>Thermo Scientific™ Substrates.</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor alpha.</td>
</tr>
<tr>
<td>V/Q</td>
<td>Ventilation /Perfusion.</td>
</tr>
<tr>
<td>VHL/E3</td>
<td>Von Hippel-Lindau tumour suppressor protein.</td>
</tr>
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<td>Vs</td>
<td>Versus.</td>
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<td>Correlation between EPO hormone level and both Hemoglobin and HCT levels in groups of COPD patients.</td>
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<td>Correlation between EPO hormone level and Oxygen saturation during exacerbation in COPD patients.</td>
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<td>Correlation between EPO hormone level and Oxygen saturation during remission in COPD patients.</td>
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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. *(GOLD, 2016)*

Acute exacerbation of COPD was defined as an acute event characterized by aworsening of the patients respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications. *(GOLD, 2016).*

It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD. However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis. *(Similowski T, Agusti A et al., 2006, Attaran D et al., 2009).*

Erythropoietin is an endogenous glycoprotein hormone that serves as the primary stimulus for erythropoiesis. The kidney is the primary site of EPO production, but the liver also produces the hormone. EPO acts in the bone marrow, where it promotes terminal differentiation of progenitor cells into erythrocytes *(Erslev A J et al., 1991).*

Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase *(Jelkmann W et al., 1992).*
Ninety percent of EPO is produced in the peritubular cells of the adult kidney in response to a decrease in tissue oxygenation. (Koury T, Bondurant M C et al., 1988).
AIM OF THE WORK

The aim of this work is to assess the changes in erythropoietin in COPD patients during exacerbation and after remission.


**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

*Definitions:*

The guidelines published by the *American Thoracic Society (1995)* defined COPD as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; and may be partially reversible.

*British Thoracic Society (1997)* defined COPD as a slowly progressive disorder characterized by airways obstruction (reduced FEV1 and FEV1/FVC ratio), which did not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator or other therapy.

The Global Initiative for Chronic Obstructive Lung Disease (*GOLD, 2003*) stated that it is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

*GOLD, (2011)* stated that (COPD) is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases. Exacerbations and co morbidities contribute to the overall severity in individual patients.
**GOLD, (2016):** COPD is a common preventable and treatable disease, is characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

**Chronic bronchitis** is defined as the presence of chronic productive cough on most days for 3 months, in each of two consecutive years, in a patient in whom other causes of chronic cough have been excluded (Jud, 1998).

**Emphysema** is defined as abnormal, permanent enlargement of the airspaces, distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis (Snider et al., 1985).

Extra pulmonary effects of COPD include, weight loss, nutritional abnormalities, skeletal muscle dysfunction, risk for myocardial infarction, angina, osteoporosis, bone fractures, depression and sleep disorders (Van Weel and Schellevis, 2006).

**Acute exacerbation of chronic obstructive pulmonary disease** is defined as a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates change in regular medication (Rodriguez-Roisin, 2000).

**Acute exacerbation of chronic obstructive pulmonary disease** is defined as acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medications **GOLD, (2016).**
Factors that influence disease development and progression:

Risk factors for COPD (Gold 2016):

- Genes.
- Inhalation exposure.
  a) Tobacco smoking.
  b) Occupational dusts.
  c) Indoor air pollution.
  d) Outdoor air pollution.
- Oxidative stress.
- Age and Gender.
- Respiratory infection.
- Socioeconomic status.
- Nutrition.
- Comorbidities.
- Asthma and bronchial hyperreactivity.
- Chronic Bronchitis.
- Previous tuberculosis.
- Lung growth and development.

Genes:

COPD is a polygenic disease and a classic example of gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin (Stoller and Aboussouan, 2005), a major circulating inhibitor of serine proteases. Although alpha-1 antitrypsin deficiency is relevant to only a small part of the world’s population, it illustrates the interaction between genes and
environmental exposures leading to COPD. A significant familial risk of airflow obstruction has been observed in smoking siblings of patients with severe COPD suggesting that genetic factors could influence this susceptibility (MacCloskey et al., 2001). Through genetic linkage analysis, several regions of the genome have been identified that likely contain COPD susceptibility genes, including chromosome 2q (Silverman et al., 2002). Genetic association studies have implicated a variety of genes in COPD pathogenesis, including transforming growth factor beta 1 (TGF-β1) (Wu et al., 2004) microsomal epoxide hydrolase 1 (mEPHX1) (Smith and Harrison, 1997) and tumor necrosis factor alpha (TNF-α) (Huang et al., 1997), the gene encoding matrix metallopropteinase 12 (MMP12), a role of the gene for the alpha-nicotinic acetylcholine receptor as well as the hedge-hog interacting protein gene. However, the results of these genetic association studies have been largely inconsistent, and functional genetic variants influencing the development of COPD (other than alpha-1 antitrypsin deficiency) have not been definitively identified (Silverman et al., 2002).

**Inhalational Exposures:**

Because individuals may be exposed to a variety of different types of inhaled particles over their life time, it is helpful to think in terms of the total burden of inhaled particles. Of the many inhalational exposures that may be encountered over a lifetime, only tobacco smoke (Burrows et al., 1977) and occupational dusts and chemicals (vapors, irritants, and fumes) (Matheson et al., 2005) are known to cause COPD on their own. Tobacco smoke and occupational exposures also appear to act additively to increase the risk of developing COPD. However, this may reflect an inadequate data base from populations who are exposed to other risk
Factors, such as heavy exposures to indoor air pollution from poorly vented biomass cooking and heating (*GOLD 2016*).

**A. Tobacco Smoke:**

Cigarette smoking is by far the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than non-smokers. Pipe and cigar smokers have greater COPD morbidity and mortality rates than non-smokers, although their rates are lower than those for cigarette smokers (*Anthonisen et al., 2002*).

The risk for COPD in smokers is dose-related (*Burrows et al., 1977*). Age at starting to smoke, total pack/years smoked, and current smoking are also risk factors for COPD (*Jindal et al., 2006*). Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms and COPD (*Eisner et al., 2005*) by increasing the lungs total burden of inhaled particles and gases (*Dayal et al., 1994*).

**B. Occupational Dusts and Chemicals:**

Occupational exposures to organic and inorganic dusts and chemical agents and fumes are an under appreciated risk factor for COPD (*Hnizdo et al., 2004*).
C. Indoor air pollution:

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (especially among women in developing countries) continues to grow (Sezer et al., 2006).

Indoor air pollution is estimated to kill two million women and children each year (Smith, 1999).

D. Outdoor air pollution:

The role of outdoor air pollution in causing COPD is unclear; it has also been difficult to assess the effects of single pollutants in long-term exposure to atmospheric pollution. However, air pollution from fossil fuel combustion, primarily from motor vehicle emissions in cities, is associated with decrements of respiratory function (Abbey et al., 1998).

Lung Growth and Development:

Lung growth is related to processes occurring during gestation, birth, and exposures during childhood (Stein et al., 1997). Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD (Tager et al., 1988).

There is positive association between birth weight and FEV1 in adulthood (Lawlor et al., 2005).
Oxidative Stress:

Oxidative stress not only produces direct injurious effects in the lungs but also activates molecular mechanisms that initiate lung inflammation. Thus, an imbalance between oxidants and antioxidants is considered to play a role in the pathogenesis of COPD (MacNee, 2005).

Gender:

Studies from developed countries (National Heart, Lung, and Blood Institute, 2004) showed that the prevalence of the disease is now almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men (Anthonisen et al., 1994).

Infections:

Infections (viral and bacterial) may contribute to the pathogenesis and progression of COPD (Retamales et al., 2001), and the bacterial colonization associated with airway inflammation (Sethi et al., 2006). HIV infection has been shown to accelerate the onset of smoking-related emphysema (Diaz et al., 2000).

Nutrition:

Malnutrition and weight loss can reduce respiratory muscle strength and endurance, apparently by reducing both respiratory muscle mass and the strength of the remaining muscle fibers (Wilson et al., 1989). Lung CT scans of women chronically malnourished because of anorexia nervosa showed emphysema-like changes (Coxson et al., 2004).
Socioeconomic status:

COPD may be inversely related to socioeconomic status (Prescott et al., 1999).

It may reflect exposures to air pollutants, crowding or poor nutrition (US Centers for Disease Control and Prevention, 1995).

Comorbidities:

Asthma may be a risk factor for the development of COPD, although the evidence is not conclusive. A longitudinal study of people with asthma found that around 20% of subjects developed functional signs of COPD; irreversible airflow limitation (Vonk et al., 2003).
PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

PATHOLOGY:

Pathological changes characteristic of COPD are found in the proximal airways (trachea and bronchi > 2 mm internal diameter), peripheral airways, lung parenchyma, and pulmonary vasculature. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair that contribute to airway obstruction (Hogg and Timens, 2009).

Bronchial glands hypertrophy and goblet cell metaplasia occurs. This results in chronic bronchitis and excessive mucous production (Reid, 1960).

Airway wall changes include squamous metaplasia of the airway epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue (Saetta et al., 2001).

Different inflammatory cells predominate in different compartments of the central airways. In the airways wall these are lymphocytes, predominantly of the CD8+ type, but as the disease progresses neutrophils also become prominent (O'Shaughnessy et al., 1997). In the airspaces, in addition to lymphocytes, neutrophils and macrophages can also be identified (Pesci et al., 1998).

Bronchiolitis is present in the peripheral airways at an early stage of the disease (Niewoehner et al., 1974).
There is pathological extension of goblet cells and squamous metaplasia in the peripheral airways (Cosio et al., 1978).

The inflammatory cells in the airway wall and airspaces are similar to those in the larger airways (Saetta et al., 1998).

As the disease progresses, there is fibrosis and increased deposition of collagen and scar tissue formation in the airway walls, that narrows the lumen and produces fixed airways obstruction (Rennard, 1999).

Increased inflammatory response and exudate correlated with disease severity (Hogg et al., 2004).

**Figure (1):** Histologic features of chronic bronchitis. (A) A section of bronchiole wall with luminal accumulation of mucous, goblet cell hyperplasia, basement membrane thickening (arrow), and scattered mononuclear inflammatory cells. (B) A bronchial wall with squamous metaplasia of the luminal epithelium (arrow head) and hyperplasia of the subepithelial seromucinous glands (arrow), (Bernard et al., 2011).
Lung parenchyma (respiratory bronchioles and alveoli)

The most common type of parenchymal destruction in COPD patients is the centrilobular form of emphysema. As a result of emphysema there is a significant loss of alveolar attachments, which contributes to peripheral airway collapse (Lamb et al., 1993).

There are two major types of emphysema, according to the distribution within the acinus: 1) centrilobular (which involves dilatation and destruction of the respiratory bronchioles); and 2) panacinar emphysema (which involves destruction of the whole of the acinus). The former is the most common type of emphysema in COPD and is more prominent in the upper zones, while the latter predominates in patients with α1-antitrypsin deficiency and is more prominent in the lower zones (Hogg, 2004).

In the early stages of the disease, these are microscopic lesions. During the course of the disease, they may progress to macroscopic lesions or bullae (defined as an emphysematous space >1 cm in diameter). The inflammatory cell profile in the alveolar walls and the airspaces is similar to that described in the airways and persists throughout the course of the disease (Finkelstein et al., 1995).
One of the perplexing features of COPD is that smoldering inflammation and slow progressive destruction of the lung parenchyma often continue for decades after cessation of smoking (Stewart and Voekel, 2008).

**Pulmonary vasculature:**

Pulmonary vascular changes begin early during the course of the disease (Peinado et al., 1999). Initially, these changes are characterised by thickening of the vessel wall and endothelial dysfunction (Wright et al., 1983). These are followed by increased vascular smooth muscle and infiltration of the vessel wall by inflammatory cells, including macrophages and CD8+ T lymphocytes (Peinado et al., 1999).

In advanced stages of the disease, there is collagen deposition and emphysematous destruction of the capillary bed. Eventually, these structural changes lead to pulmonary hypertension and right ventricular dysfunction (cor pulmonale) (Wright et al., 2005).

**PATHOGENESIS:**

The inflammation in the respiratory tract of patients appear to be a modification of the inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplified inflammation are not yet understood but may be genetically determined. Patients can clearly develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown. Oxidative stress and an excess of proteinases in the lung further modify lung inflammation. Together, these mechanisms lead to the characteristic pathological changes in COPD. Lung inflammation persists after smoking.
cessation through unkown mechanisms, although autoantigens and persistent microorganisms may play a role (cosio et al., 2009).

A. Inflammation:

COPD is characterized by the presence of a chronic low grade systemic inflammatory response which is not significantly related to indices of lung function. Furthermore during acute exacerbation of COPD increased levels of acute phase proteins (C-reactive protein and lipopolysaccharide binding protein) are found (Dentener et al., 2001).

1. Inflammatory Cells:

COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes (Barnes et al., 2003). These cells release inflammatory mediators and interact with structural cells in the airways and lung parenchyma.

   a) Neutrophils: Increased in sputum of normal smokers. Further increased in COPD and related to disease severity. Few neutrophils are seen in tissues (Di Stefano et al., 2009). They may be important in mucus hypersecretion and through release of proteases (Stockley, 2002).

   b) Macrophages: Greatly increased in number are seen in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid. They produce increased inflammatory mediators and proteases in COPD patients in response to cigarette smoke and may show defective phagocytosis (Barnes, 2004a).

   c) T lymphocytes: Both CD4+ and CD8+ cells are increased in the airway wall and lung parenchyma, with increased CD8+:CD4+...
ratio (Baraldo et al., 2004). Increased CD8+ T cells (Tc1) and Th1 cells which secrete interferon-γ and express the chemokine receptor CXCR3. CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction (Chrysofakis et al., 2004).

d) **B lymphocytes:** Increased in peripheral airways and within lymphoid follicles, possibly as a response to chronic colonization and infection of the airways (Hogg et al., 2004). The increase in B-cell number may also reflect a role for autoimmune responses as a source of autoantibodies, and this is also supported by the reduced numbers of T-regulatory cells reported in lungs of COPD patients (Lee et al., 2007).

e) **Eosinophils:** Increased eosinophil proteins in sputum and increased eosinophils in airway wall during exacerbations (GOLD 2011).

f) **Epithelial cells:** May be activated by cigarette smoke to produce inflammatory mediators, including eicosanoids, cytokines, and adhesion molecules (Mills et al., 1999).

### 2-**Inflammatory Mediators:**

The wide variety of inflammatory mediators that have been shown to be increased in COPD patients attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors) (Barnes, 2004 b).
Many inflammatory mediators are increased in COPD, including:

- Leukotriene B4, a neutrophils and T cell chemoattractant which is produced by macrophages, neutrophils, and epithelial cells (Hill et al., 1999).
- Chemotactic factors such as the CXC chemokines interleukin 8 and growth related oncogene α, which are produced by macrophages and epithelial cells. These attract cells from the circulation and amplify pro-inflammatory responses (Spruit et al., 2003).
- Pro-inflammatory cytokines such as tumour necrosis factor α and interleukins 1β and 6 (Broekhuizen et al., 2005).
- Growth factors such as transforming growth factor β, which may cause fibrosis in the airways either directly or through release of another cytokine, (connective tissue growth factor) (Gold 2011).
- Osteopontin is recently discovered to play an important role in the pathogenesis of COPD (Schneider et al., 2010).

B. Oxidative stresses:

Oxidative stress may be an important amplifying mechanism in COPD (Rahman, 2005). Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients. Oxidants are generated by cigarette smoke and other inhaled particulates, and released from activated inflammatory cells such as macrophages and neutrophils (Bourdin et al., 2009).

Oxidative stress has several adverse consequences in the lungs, including activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion, and stimulation of increased plasma
Review of literature

exudation. Many of these adverse effects are mediated by peroxynitrite, which is formed via an interaction between superoxide anions and nitric oxide. In turn, the nitric oxide is generated by inducible nitric oxide synthase, which is expressed in the peripheral airways and lung parenchyma of COPD patients. Oxidative stress may also account for a reduction in histone deacetylase activity in lung tissue from COPD patients, which may lead to enhanced expression of inflammatory genes and also a reduction in the anti-inflammatory action of glucocorticosteroids (Ito et al., 2005). There may also be a reduction in endogenous antioxidants in COPD patients as a result of reduction in a transcription factor called Nrf2 that regulates many antioxidant genes (Rahman et al., 2005).

C. Protease-Antiprotease Imbalance:

There is evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other. Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is an important feature of emphysema (Baraldo et al., 2007). The major proteinases include Serine proteases, Neutrophil elastase, Cathepsin G, Proteinase 3, Cysteine proteinases, Cathepsins B, K, L, S, Matrix metalloproteinases (MMPs), MMP-8, MMP-9, and MMP-12. On the other hand, the major antiproteinases include alpha-1 antitrypsin, alpha-1 antichymotrypsin, Secretory leukoprotease inhibitor, Elafin, Cystatins, Tissue inhibitors of MMP 1-4 (TIMP1-4) (ATS/ERS, 2004).
Differences in Inflammation between COPD and Asthma:

Although both COPD and asthma are associated with chronic inflammation of the respiratory tract, there are differences in the inflammatory cells and mediators involved in the two diseases, which in turn account for differences in physiological effects, symptoms, and response to therapy. Some patients with COPD have features consistent with asthma and may have a mixed inflammatory pattern with increased eosinophils (Fabbri et al., 2003).

PATHOPHYSIOLOGY:

The previous pathogenic mechanisms result in the pathological changes found in COPD. These in turn result in physiological abnormalities: mucous hypersecretion and ciliary dysfunction, airflow obstruction and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects (MacNee, 2007).

1-Mucous hypersecretion and ciliary dysfunction:

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, it is due to mucous metaplasia with increased numbers of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Ciliary dysfunction is due to squamous metaplasia of epithelial cells and results in an abnormal mucociliary escalator and difficulty in expectorating. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects
through the activation of epidermal growth factor receptor (EGFR) 
(*Burgel et al., 2004*).

2-Airflow obstruction and hyperinflation or air trapping:

The main site of airflow obstruction occurs in the small conducting 
airways that are < 2 mm in diameter. This is because of inflammation and 
narrowing (airway remodeling), inflammatory exudates in the small 
airways, loss of the lung elastic recoil (due to destruction of alveolar 
walls) and destruction of alveolar support (from alveolar attachments) 
(*MacNee, 2007*).

The airway obstruction progressively traps air during expiration, 
resulting in hyperinflation at rest and dynamic hyperinflation during 
exercise. Dynamic hyperinflation is closely linked to shortness of breath 
(dyspnea) in COPD (*O'Donnell, 2001*).

3-Gas Exchange Abnormalities:

Gas exchange abnormalities result in hypoxemia and hypercapnia. 
In general, gas transfer worsens as the disease progresses. The severity of 
emphysema correlates with arterial PO2 and other markers of ventilation-
perfusion imbalance. Peripheral airway obstruction also results in 
ventilation-perfusion imbalance and combines with ventilatory muscle 
impaired function in severe disease to reduce ventilation, leading to 
carbon dioxide retention (*Rodriguez-Roisin and MacNee, 1998*).

4-Pulmonary hypertension:

Mild to moderate pulmonary hypertension may develop late in the 
course of COPD and is due to hypoxic vasoconstriction of small 
pulmonary arteries, eventually resulting in structural changes that include
intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure (cor pulmonale) (*Barbera et al.*, 2003).

5- **Exacerbations:**

During respiratory exacerbations there is increased hyperinflation and gas trapping, worsening of v/q abnormalities, which can result in hypoxemia (*Barbera et al.*, 1997).

6- **Systemic features:**

It is increasingly recognized that many patients with COPD have comorbidities that have a major impact on quality of life and survival (*Barnes and Celli et al.*, 2009) Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange (*Barr et al.*, 2010). Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, metabolic syndrome, and depression.
Diagnosis of COPD

1-History:

The diagnosis of COPD should be considered in anyone who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease such as regular tobacco smoking (Rabe et al., 2007). No single symptom or sign can adequately confirm or exclude the diagnosis of COPD although COPD is uncommon under the age of 40 years (Holleman and Simel, 1995).

A detailed medical history of a new patient known or thought to have COPD should assess (Currie and Legge, 2007):

- Patient’s exposure to risk factors particularly with regard to exposure to dusts, chemicals, patient’s current smoking status and the number of smoking pack years.
- Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases such as tuberculosis.
- Family history of COPD.
- Pattern of symptom development (dyspnea, cough, sputum production and chest tightness).
- History of exacerbations or previous hospitalizations for respiratory disorder.
- Presence of comorbidities which may also contribute to restriction of activity.
2-Assessment of Symptoms:

Since COPD may be diagnosed at any stage, any of the symptoms described below may be present in a patient presenting for the first time.

a) Dyspnea:

The hallmark symptom of COPD, typical COPD patients describe their dyspnea as a sense of increased effort to breath, heaviness, air hunger, or gasping (Simon et al., 1990).

As lung function deteriorates, breathlessness becomes more intrusive, and patients may notice that they are unable to walk at the same speed as other people of the same age or carry out activities that require the use of accessory respiratory muscles (e.g., carrying grocery bags) (Celli et al., 1986).

The functional limitation from breathlessness due to COPD can be quantified easily in clinical practice. There are different grading systems for dyspnea but the most applicable is that of Medical Research Council.

Table (1): Medical Research Council grading of functional limitation due to dyspnea (Bestall et al., 1999):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptom complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;Only get breathless with strenuous exercise.&quot;</td>
</tr>
<tr>
<td>2</td>
<td>&quot;Get short of breath when hurrying on the level or walking up a slight hill.”</td>
</tr>
<tr>
<td>3</td>
<td>&quot;Walk slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at his own pace on the level.&quot;</td>
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</table>
| 4 | "Stop for breath after walking about 100 yards or after a few minutes on the level."
| 5 | "Patient too breathless to leave the house" or "patient breathless when dressing."

**COPD assessment test (CAT):** an 8-item measure of health status impairment in COPD, the score ranges from 0-40 (*Jones et al, 2009*)

<table>
<thead>
<tr>
<th>I never cough</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>I cough all the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>My chest is full of phlegm (mucus)</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>My chest feels very tight</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>When I walk up a hill or one flight of stairs I am very breathless</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>I am very limited doing activities at home</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>I am not at all confident leaving my home because of my lung condition</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>I don’t sleep soundly because of my lung condition</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>I have no energy at all</td>
</tr>
</tbody>
</table>
b) Cough:

Chronic cough, often the first symptom of COPD to develop (Georgopoulas et al., 1991).

Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive (Burrows et al., 1965).

c) Sputum production:

COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. The presence of purulent sputum reflects an increase in inflammatory mediators (Hill et al., 1999), and its development may identify the onset of an exacerbation (Stockley et al., 2000).

d) Wheezing and chest tightness:

These are nonspecific symptoms that may be present in Stage I: Mild COPD, but are more characteristic of asthma or Stage III: Severe COPD and Stage IV: Very Severe COPD. But absence of wheezing or chest tightness does not exclude a diagnosis of COPD (GOLD 2016).

3- Assessment of Exacerbation Risk:

Exacerbation of COPD is defined as an acute event characterized by worsening of patient’s respiratory symptoms that is beyond normal day-to-day variations and that leads to a change in medications (Celli and Bames et al, 2007).
The best predictor of having frequent exacerbations (2 or more per year) is a history of previous treated event, in addition worsening airflow limitations is associated with an increasing prevalence of exacerbation and risk of death (Hurst et al, 2010).

4- Combined COPD assessment (Gold 2016):

Because severity of airflow limitation is not the only factor that govern out-come in COPD combined assessment including different factors relating to overall severity has been introduced in the new GOLD guidelines (2015) incorporating patients symptoms, severity of airflow limitation and frequency of exacerbation.

Figure:(3)

Patient group A : less symptoms, low risk

Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) &/or 0-1 exacerbation per yr and mMRC grade 0-1 or CAT <10.
Patient group B: more symptoms, low risk

Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) \&/or 0-1 exacerbation per yr and mMRC grade ≥2 or CAT ≥10.

Patient group C: less symptoms, high risk

Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) \&/or ≥2 exacerbation per yr and mMRC grade < 2 or CAT < 10.

Patient group D: more symptoms, high risk

Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) \&/or ≥2 exacerbation per yr and mMRC grade ≥2 or CAT ≥10.

3-Physical Examination:

a) General:

COPD may show signs consistent with cor pulmonale (raised jugular venous pressure, loud P2 heart sounds due to pulmonary hypertension, tricuspid regurgitation, pitting peripheral oedema, and hepatomegaly). Skeletal muscle wasting and cachexia, may be present in those with advanced disease. Finger clubbing is not found in COPD, and its presence should prompt thorough evaluation to exclude a cause such as lung cancer, bronchiectasis, or idiopathic pulmonary fibrosis (Currie and Legge, 2007).
b) Local:

Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred (*Kesten and Chapman, 1993*).

**Inspection (**GOLD 2011**):**

- Central cyanosis.
- Barrel-shaped chest, and protruding abdomen.
- Flattening of the hemi-diaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, and widening of the xiphisternal angle (Hoover's sign).
- Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow.
- Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying.
- Ankle or lower leg edema can be a sign of right heart failure.

**Palpation and percussion:**

- Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without being enlarged (*Celli et al., 2004*).

**Auscultation:**

- Patients with COPD often have reduced breath sounds (*Badgett et al., 1993*).
- The presence of wheezing during quiet breathing is a useful pointer to airflow limitation (*ATS/ERS 2004*).
4- Investigations:

a) Measurement of Airflow Limitation (Spirometry):

The diagnosis of COPD is confirmed by spirometry. Spirometry measures the forced expiratory volume in one second (FEV1) which is the greatest volume of air that can be breathed out in the first second. Forced vital capacity (FVC) is the greatest volume of air that can be breathed out in a fastest and deepest breath. Normally at least 70% of the FVC comes out in the first second (i.e. the FEV1/FVC ratio is >70%). In COPD, this ratio is less than normal, (i.e. FEV1/FVC ratio is <70%) even after a bronchodilator medication has been given (Rabe et al., 2007).

Table 2: Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1 (GOLD 2016)

<table>
<thead>
<tr>
<th>FEV1/FVC &lt; 0.70</th>
<th>Stage I: Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 ≥80% predicted</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>FEV1/FVC &lt; 0.70</th>
<th>Stage II: Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% ≤FEV1 &lt; 80% predicted</td>
<td></td>
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<table>
<thead>
<tr>
<th>FEV1/FVC &lt; 0.70</th>
<th>Stage III: Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% ≤FEV1 &lt; 50% predicted</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEV1/FVC &lt; 0.70</th>
<th>Stage IV: Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 &lt; 30% predicted</td>
<td></td>
</tr>
</tbody>
</table>

b) Reversibility testing:

Reversibility testing to oral corticosteroids or inhaled bronchodilator is not always necessary, but it should be performed if asthma is thought likely or if the response to treatment (β2 agonists or corticosteroids) is surprisingly good. However, asthma can often be
distinguished from COPD by the history, examination, and baseline spirometry. More detailed lung function measurements such as lung volumes (total lung capacity and residual volume), gas transfer coefficient, and walking distance in six minutes can be done if diagnostic doubt persists or more thorough evaluation is required (Currie and Legge, 2007).

c) Peak expiratory flow:

Solitary peak expiratory flow readings can seriously underestimate the extent of airflow obstruction, while serial monitoring of peak expiratory flow is not generally useful in the diagnosis of COPD (Currie and Legge, 2007).

d) Imaging:

1-Chest X-ray:

It is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation, hyperlucency of the lungs, and rapid tapering of the vascular markings (Pauwels et al., 2001).

2-Computed tomography (CT):

Not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution computed tomography (HRCT) scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability (Fishman et al., 2008).
e) Additional Investigations:

1-Arterial blood gas measurement:

In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with FEV1 < 50% predicted or with clinical signs suggestive of respiratory failure or right heart failure \textit{(GOLD 2016)}.

Screening patients by pulse oximetry and assessing arterial blood gases in those with oxygen saturation (SaO2) < 92% is a useful way of selecting patients for arterial blood gas measurement \textit{(Roberts et al., 1993)}.

2-Alpha-1 antitrypsin deficiency screening:

In patients of Caucasian descent who develop COPD at a young age (< 45 years) or who have a strong family history of the disease. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency \textit{(Gold 2016)}.

3-Hematocrit:

Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers \textit{(Calverly et al., 1982)}, and can be identified by hematocrit > 55% \textit{(Siafakas et al., 1995)}.

A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment \textit{(Chambellan et al., 2005)}.

4- Electrocardiography (ECG):

Electrocardiography may show typical changes of chronic right sided heart strain. However, echocardiography is more sensitive in detecting tricuspid valve incompetence, as well as right atrial and
ventricular hypertrophy. It is also useful in determining whether left ventricular dysfunction is present (Currie and Legge, 2007).

5-Exercise testing:

Cardiopulmonary exercise tests may be useful to differentiate between breathlessness resulting from cardiac or respiratory disease, and may help to identify other causes of exercise limitation (eg, hyperventilation, musculoskeletal disorder) (Australian Lung Foundation, 2010).

6-Sleep studies:

Specialist referral is recommended for COPD patients suspected of having a coexistent sleep disorder or with hypercapnia or pulmonary hypertension in the absence of daytime hypoxaemia, right heart failure or polycythaemia (Australian Lung Foundation, 2010).

7-Ventilation and perfusion scans:

The ventilation and perfusion (V/Q) scan may be difficult to interpret in COPD patients, because regional lung ventilation may be compromised leading to matched defects. If pulmonary emboli are suspected, a CT pulmonary angiogram may be more useful. Quantitative regional V/Q scans are helpful in assessing whether patients are suitable for lung resection and lung volume reduction surgery (Australian Lung Foundation, 2010).
Differential Diagnosis

Table 3: Differential diagnosis of COPD (*GOLD 2016*)

<table>
<thead>
<tr>
<th>Suggestive Features</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset in mid-life.</td>
<td>COPD</td>
</tr>
<tr>
<td>Symptoms slowly progressive.</td>
<td>COPD</td>
</tr>
<tr>
<td>Long history of tobacco smoking.</td>
<td>COPD</td>
</tr>
<tr>
<td>Dyspnea during exercise.</td>
<td>COPD</td>
</tr>
<tr>
<td>Largely irreversible airflow limitation.</td>
<td>COPD</td>
</tr>
<tr>
<td>Onset early in life (often childhood).</td>
<td>Asthma</td>
</tr>
<tr>
<td>Symptoms vary from day to day.</td>
<td>Asthma</td>
</tr>
<tr>
<td>Symptoms at night/early morning.</td>
<td>Asthma</td>
</tr>
<tr>
<td>Allergy, rhinitis, and/or eczema also present.</td>
<td>Asthma</td>
</tr>
<tr>
<td>Family history of atopy.</td>
<td>Asthma</td>
</tr>
<tr>
<td>Largely reversible airflow limitation.</td>
<td>Asthma</td>
</tr>
<tr>
<td>Fine basilar crackles on auscultation.</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>Chest X-ray shows dilated heart, pulmonary edema.</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>Pulmonary function tests indicate volume restriction, not airflow limitation.</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>Large volumes of purulent sputum, clubbing.</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Commonly associated with bacterial infection.</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Coarse crackles on auscultation.</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Chest X-ray/CT shows bronchial dilatation, bronchial wall thickening.</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Onset all ages</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Chest X-ray shows lung infiltrate.</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Microbiological confirmation.</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>High local prevalence of tuberculosis.</td>
<td>Tuberculosis</td>
</tr>
</tbody>
</table>
Onset in younger age, nonsmokers. 
May have history of rheumatoid arthritis or fume exposure. 
CT on expiration shows hypodense areas. 

<table>
<thead>
<tr>
<th>Obliterative Bronchiolitis</th>
</tr>
</thead>
</table>

Most patients are male and nonsmokers. 
Almost all have chronic sinusitis. 
Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation. 

<table>
<thead>
<tr>
<th>Diffuse Panbronchiolitis</th>
</tr>
</thead>
</table>

**Table 4: Characteristics of inflammation in COPD and bronchial asthma (GOLD 2003)**

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cells</strong></td>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td></td>
<td>Large increase in macrophages</td>
<td>Small increase in macrophages</td>
</tr>
<tr>
<td></td>
<td>Increase in CD8 T lymphocytes</td>
<td>Increase in CD4 Th2 lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activation of mast cells</td>
</tr>
<tr>
<td><strong>Mediators</strong></td>
<td>LTB4</td>
<td>LTD4</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>IL-4, IL-5</td>
</tr>
<tr>
<td></td>
<td>TNF-alpha</td>
<td></td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Sequamous metaplesia of epithelium</td>
<td>Fragile epithelium</td>
</tr>
<tr>
<td></td>
<td>Parenchymal destruction</td>
<td>Thickening of basement membrane</td>
</tr>
<tr>
<td></td>
<td>Mucus metaplesia</td>
<td>Mucus metaplasia</td>
</tr>
<tr>
<td></td>
<td>Glandular enlargement</td>
<td>Glandular enlargement</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>Glucocorticoids have little or no effects</td>
<td>Glucocorticoids inhibit inflammation</td>
</tr>
</tbody>
</table>
Systemic features and co-morbidities in COPD

It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases (Agusti et al., 2005).

Cachexia is commonly seen in patients with severe COPD. There may be loss of skeletal muscle mass and weakness as a result of increased apoptosis and/or muscle disuse. Patients with COPD also have increased likeliness of having osteoporosis, depression and chronic anemia (Similowski et al., 2006).

Increased concentrations of inflammatory mediators, including TNF-α, IL-6, and oxygen-derived free radicals, may mediate some of these systemic effects. There is an increase in the risk of cardiovascular diseases, which is correlated with an increase in C-reactive protein (CRP) (Gan et al., 2004).

The systemic effects of COPD include:

1-Cardiovascular Effects:

Cardiovascular disease is a major cause of mortality and morbidity in patients with COPD. Although there are common causal factors including smoking and sedentarism, the increase in cardiovascular disease is independent of these known risk factors (Mannino et al., 2008). Four separate entities within CVD will be considered: ischemic heart disease, heart failure, atrial fibrillation and hypertension.

Ischemic heart disease (IHD): IHD is increased in COPD there is evidence that concomitant COPD increases morbidity and mortality
among patients with IHD (Campo et al., 2013) and that myocardial injury is overlooked and IHD is therefore under-diagnosed in COPD patients (Brekke et al., 2008). Systemic inflammation may predispose to atherosclerotic plaques, which may account for the high prevalence of myocardial infarction in patients with COPD (Barnes, 2010).

Treatment of IHD in patients with COPD: IHD should be treated according to usual guildlines, in a significant proportion of patients with IHD a beta - blocker will be indicated , treatment with selective beta-blockers is considered safe in few short-term studies (Mainguy et al., 2012).

Treatment of COPD in patients with IHD: COPD should be treated as usual it seems reasonable to avoid especially high doses of beta-agonists (Calverley et al., 2010).

Heart failure (HF): heart failure is a common comorbidity in COPD. Roughly 30% of patients with stable COPD will have some degree of HF (Rutten et al., 2005), and worsening of HF is a significant differential diagnosis to an exacerbation of COPD. Approximately 30% of patients in a HF clinic have COPD, and comorbid COPD is often the cause of admission for acute HF with significant implications for prognosis as FEV1 is a strong predictor of mortality in HF (Iversen et al., 2010). HF, COPD and asthma may be confused because of the common cardinal symptom of breathlessness.

Treatment of HF in patients with COPD: HF should be treated according to usual HF guidelines. Studies have shown that treatment with bisoprolol in HF with concomitant COPD decreased FEV1 but without deleterious effects on symptoms and quality of life and that selective
beta1-blocker is preferable to non selective beta1-blocker in HF with COPD. Bisoprolol was superior to carvedilol on respiratory parameters (Lainscak et al., 2011).

Treatment of COPD in patients with HF: should be treated as usual (Calverley et al., 2010), an observational study found an increased risk of death and hospitalization among patients with HF treated with inhaled beta-agonists, possibly indicating a need for close follow up of patients with severe HF who are on this treatment for COPD (Au DH et al., 2003).

**Atrial fibrillation (AF):** AF is the most frequent cardiac arrhythmia and COPD patients have an increased incidence of AF (Buch et al., 2003).

Treatment of AF in patients with COPD: should be treated according to usual guidelines.

Treatment of COPD in patients with AF: should be treated as usual but high doses of beta2-agonists can make appropriate heart rate control difficult.

**Hypertension:** is the most frequent occurring comorbidity in COPD and has implications for prognosis (Fabbri et al., 2008). Several studies have shown that COPD patients have increased arterial stiffness, which may explain the epidemiological link between reduced FEV1 (forced expiratory volume in 1 second) and cardiovascular mortality (Sabit et al., 2007).
Recent study was not able to demonstrate any defect in endothelial function in COPD patients with arterial stiffness, suggesting that it may be due to an abnormality in the arterial wall (Maclay et al., 2009).

Treatment of hypertension in patients with COPD: should be treated as usual, use selective beta1-blocker instead of beta-blocker.

Treatment of COPD in patients with hypertension: should be treated as usual.

**Polycythaemia:** is the major haematological complication predisposing to vascular events. Hypoxia, hypercapnia and Polycythaemia together or alone lead to impaired neuropsychiatric performance (Agusti, 2005).

2-Bones:

Osteoporosis is a major comorbidity in COPD (Fabbri et al., 2008). May be more closely related to emphysema than other subgroups of COPD (McAllister et al., 2007). Osteoporosis is associated with decreased body mass index and low fat-free mass (Bolton et al., 2008). The incidence of osteoporosis and osteopenia was higher the more the severity of COPD (EL-Khattib et al., 2006). There are several proposed mechanisms:

a) **Smoking:**

Smoking has been recognized as a contributing factor to bone loss (Jensen 1986), smoking also is considered as a risk factor for osteoporosis in men and women (Slemenda et al., 1992).
Review of literature

b) **Systemic and inhaled corticosteroids:**

Despite beneficial effects on lung function and well being of the patient, its use was associated with side effects, one of which is osteoporosis (*Gross, 2001*). Inhaled triamcinolone is associated with osteoporosis more than budesonid or fluticasone (*lung health study et al., 2000*).

c) **Reduced skeletal muscle mass:**

Skeletal muscle dysfunction in COPD is due to reduced mobility due to shortness of breath and steroid myopathy became more obvious in patients with severe disease (*Ionescu and Schoon, 2003*).

d) **Body mass index and changes in body composition:**

Weight loss and a low BMI are predictors of mortality in patients with COPD (*Wouters et al., 2002*). Loss of bone mineral density (BMD) may also occur with lumbar spine fractures reported in nearly 20% of male patients. A key feature of the patients was the stronger association of both lung disease and the link between fat free mass (FFM) and loss at the hip compared with the lumbar spine (*Bolton et al., 2004*).

e) **The role of chronic systemic inflammation:**

Increased levels of systemic inflammatory markers (TNF-α, IL-6 and CRP) have been reported in COPD, mainly in patients who lose weight and in those with low skeletal muscle mass (*Farouk, 2011*).
3-Endocrinal system:

a) Testosterone:

Anabolic hormone levels are low in COPD; it is attributed to chronic hypoxia, disease severity, smoking, corticosteroids and chronic inflammation (Kamishke et al., 1998).

Low testosterone level can predict low bone density and low muscle strength (Creutzberg and Casaburi, 2003).

b) Adipokines (leptin and adiponectin):

- Leptin:

Leptin is a peptidic hormone or adipokine produced mainly in the fat tissue, its circulating form being proportional to the fat tissue quantity in any given subject. Its effects on the energy metabolism are exerted by the hypothalamic nuclei. Leptin is also involved in lipid and glucose metabolism, synthesis of glucocorticoids and insulin, regulation of the hypothalamic–pituitary–adrenal axis, maturation of the reproductive system, hematopoiesis, angiogenesis and fetal development (Wouters et al., 2007).

Acute exacerbations of COPD may be associated with a transient increase in serum concentrations of leptin (Mahmoud, 2012). This disturbance might be induced by the systemic inflammatory response, as well as by the systemic corticosteroid treatment associated with acute COPD exacerbation (Creutzberg et al., 2000).
• **Adiponectin:**

If leptin has proinflammatory effects, it was shown that adiponectin has anti-inflammatory properties. Adiponectin has an important role in regulation of insulin sensitivity and it has a molecule composed of a globular and a collagenous domain. The globular domain of adiponectin has close structural similarities with TNF-α. Leukocyte elastase could cleave the adiponectin molecule and release this globular domain, thus activated leukocytes could interfere in adiponectin bioactivity. Adiponectin reduces TNF-α production and also its activity, inhibits IL-6 production and induces the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist, as shown in studies with animal and human models (*Masaki et al.*, 2004).

Furthermore, acute exacerbation of COPD was associated with greater serum adiponectin concentrations than stable disease in COPD patients (*Abd El-hamid, 2012*).

c) **Thyroid hormone:**

The severity of airway obstruction in COPD is associated with impairment of thyroid gland function. There is an apparent clinical resemblance between hyperthyroid state and advanced COPD. Early detection of thyroid disturbances may therefore be clinically important in COPD (*Uzun et al.*, 2007).
4-COPD and Metabolic Diseases:

There is an increased risk of diabetes in COPD patients. Systemic inflammation, and particularly the proinflammatory cytokines TNF-α and IL-6, may induce insulin resistance (Mannino et al., 2008).

Metabolic syndrome, characterised by central obesity, diabetes, hypertension, and hyperlipidaemia, is also known to occur with COPD. In a recent study of COPD patients, metabolic syndrome was found in almost half of the patients irrespective of disease stage and was associated with increased markers of systemic inflammation, including IL-6, CRP, and fibrinogen (Watz et al., 2009).

Cachexia and weight loss has also been associated with COPD, particularly in severe disease and may be related to increased concentrations of certain cytokines, such as TNF-α. There is selective loss of skeletal muscle, measured as fat-free mass, and this is associated with a selective loss of type IIA fibers (Barnes, 2010).

Gastroesophageal reflux (GERD) is a risk factor for exacerbations and is associated with worse health status. proton pump inhibitors are often used for treatment of GERD (Martinez et al., 2014).

5-Bronchiectasis and COPD:

COPD is a feature of some patients with a primary diagnosis of bronchiectasis, it is associated with longer exacerbation and increased mortality (Martinez-Garcia et al., 2013).
6-COPD and lung cancer:

Patients with COPD are 3 to 4 times more likely to develop lung cancer than are smokers with normal lung function. Lung cancer is found in 40%–70% of patients with COPD, particularly in severe disease, and is a common cause of death in COPD patients (Young et al., 2009).

The most likely explanation for the increased risk of lung cancer in COPD is the presence of chronic inflammation, with increased production of growth and angiogenic factors. Stopping smoking in COPD patients reduces but does not eliminate the risk of lung cancer, probably because inflammation persists even after smoking cessation (Anthonisen et al., 2005). Reduced lung function in patients with COPD will be a factor limiting surgical intervention for lung cancer.

7-Neurological:

Anxiety, depression and Cognitive dysfunction are increasingly recognized in patients with COPD, especially in severe disease, common to occur with younger age, females smoking, lower FEV1,cough,higher SGRQ score and a history of cardiovascular disease (Hanania et al., 2011) and this may have an important impact on self management and adherence to therapy (Hung et al., 2009). Treatment of anxiety and depression should be according to usual guidelines ,pulmonary rehabilitation has a beneficial effect on depression (Coventry et al., 2013).

The coexistence of COPD and OSA is relatively common. In this so called overlap syndrome, patients are at increased risk of pulmonary hypertension and respiratory failure related to progressive nocturnal hypoxemia (Stradling and Davies, 2004).
8-COPD and Infection:

Serious infections, especially respiratory infections, are frequently seen in patients with COPD (Benfield et al., 2008).

Treatment of infection in patients with COPD: Macrolide antibiotics increase the serum concentration of theophylline. However, repeated courses of antibiotics increase the risk for the presence of antibiotic resistant bacterial strains.

Treatment of COPD in the presence of infection:
COPD should be treated as usual but if the patient develop repeated pneumonias while on inhaled corticosteroids, this medication may be stopped in order to observe whether this medication could be the cause of repeated infections.
Treatment of COPD

1-Risk factor reduction:

a) Smoking cessation:

Smoking cessation is one of the most important factors in slowing down the progression of COPD. Once COPD has been diagnosed, stopping smoking slows down the rate of progression of the disease. Even at a late stage of the disease it can significantly reduce the rate of deterioration in lung function and delay the onset of disability and death (Anthonisen et al., 2005).

Some smokers can achieve long-term smoking cessation through "willpower" alone. However many smokers need further support to quit. The chance of successfully stopping smoking can be greatly improved through social support, engagement in a smoking cessation program and the use of drugs such as nicotine replacement therapy, bupropion and varenicline (WHO, 2008).

Pharmacotherapy for smoking cessation:

Nicotine Replacement Products: in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates (Tonnesen et al., 2006). Medical contra indications to nicotine replacement therapy include unstable coronary artery disease, untreated peptic ulcer disease, and recent myocardial infarction or stroke (Fiore et al., 1996), nausea associate nicotine shewing gum secrerations absorption ,also acidic beverages like coffee, guices, and soft drinks interfere with absorbtion of nicotine.
**Pharmacologic:** varenicline, bupropion and nortriptyline have been used in a supportive intervention program rather than on their own and increases the long term quit rates (*Tashkin et al., 2011*).

Because tobacco dependence is a chronic disease, clinicians should recognize that relapse is common and reflects the chronic nature and addiction, not failure on the part of the clinician or the patient.

**Brief strategies to help the patient willing to quit:**

- **Ask:** about tobacco use.
- **Advice:** the patient to quit.
- **Assess:** willingness of the patient to quit.
- **Assist:** aid the patient to quit.
- **Arrange:** Schedule follow up contact.

**b) Occupational exposures:**

Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (*Oroczo-Levi et al., 2006*).

**c) Air pollution:**

A person who has COPD may experience fewer symptoms if they stay indoors on days when air quality is poor (*Rabe et al., 2007*).
2-Management of stable COPD

A) Pharmacologic treatment (Table 5 and Figure 4):

Recommendations for the pharmacological treatment (*GOLD 2016*):

- Treatment tends to be cumulative with more medications being required as the disease state worsens.
- Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens.
- Individuals differ in their response to treatment and in the side effects they report during therapy.

None of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function (*Burge et al., 2000*).

1) Bronchodilators

Bronchodilators are medicines that relax smooth muscle around the airways, increasing the caliber of the airways and improving air flow. They improve the expiratory air flow and so improve emptying of the lung, tend to reduce dynamic hyperinflation at rest and during exercise and improve exercise performance (*O’Donnell et al., 2006*). They do not slow down the rate of progression of the underlying disease (*Rabe et al., 2007*).

There are three major types of bronchodilators, β2 agonists, anticholinergics and theophyllin. Anticholinergics appear to be superior to β2 agonists in COPD. Each type may be either long-acting (with an
effect lasting 12 hours or more) or short-acting (with a rapid onset of effect that does not last as long) (Salpeter et al., 2006).

Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available (GOLD 2016).

2) Corticosteroids

Corticosteroids act to reduce the inflammation in the airways, in theory reducing lung damage and airway narrowing caused by inflammation (Pinto-Plata et al., 2006). Unlike bronchodilators, they do not act directly on the airway smooth muscle and do not provide immediate relief of symptoms. Some of the more common corticosteroids in use are prednisone, fluticasone, budesonide, mometasone, and beclomethasone. Corticosteroids are used in tablet or inhaled form to treat and prevent acute exacerbations of COPD. Well-inhaled corticosteroids (ICS) have not been shown to be of benefit for people with mild COPD; however, they have been shown to decrease acute exacerbations in those with either moderate or severe COPD (Gartlehner et al., 2006).

Inhaled corticosteroids: moderate to high doses can be used. Regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations in COPD patients with FEV1 <60% predicted (Calverley et al., 2007).

Adverse effects: oral candidiasis, hoarse voice, skin bruising (Burge et al., 2000), increased risk of pneumonia (Calverley et al., 2007) , long-term use of inhaled triamcinolone acetonide reduce bone density (Johnell et al., 2002)
Combination inhaled corticosteroid/bronchodilator therapy is more effective than individual components in improving lung function and health and reducing exacerbations in patients with moderate to severe COPD (Calverley et al., 2007).

3) Other Pharmacologic Treatments:

a- Vaccines:

Influenza vaccines can reduce serious illness (Wongsurakiat et al., 2004) and death in COPD patients by about 50% (Wongsurakiat et al., 2003). Vaccines containing killed or live, inactivated viruses are recommended (Edwards et al., 1994) as they are more effective in elderly patients with COPD (Hak et al., 1998). Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years older and immunocompromised patients (Jackson et al., 2003).

b- Alpha-1 antitrypsin augmentation therapy:

In young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema. However, this therapy is very expensive, is not available in most countries (GOLD 2016).

c- Antibiotics:

There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful (Siakafas and Bouros, 1998).

d- Mucolytic (mucokinetic, mucoregulator) agents:

Oral mucolytics (ambroxol, erdosteine, carbocysteine, iodinated glycerol) are thought to reduce the viscosity of sputum in the airways
and help patients expectorate. Their regular use reduces the frequency of exacerbations of COPD (Poole and Black, 2001).

e-Antioxidant agents:

N-acetylcysteine, have been reported to reduce the frequency of exacerbations, leading to speculation that these medications could have a role in the treatment of patients with recurrent exacerbations (Hansen et al., 1994).

f-Immunoregulators (immunostimulators, immunomodulators):

Studies using an immunoregulator in COPD as phosphodiesterase 4 (PDE4) inhibitors (cilomilast and roflumilast) show a decrease in the severity and frequency of exacerbations (Li et al., 2004).

g-Antitussives.

Cough, although sometimes a troublesome symptom in COPD has a significant protective role. Thus the regular use of antitussives is not recommended in stable COPD (Irwin et al., 1998).

h-Vasodilators:

Pulmonary hypertension in COPD is associated with a poorer prognosis. Hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt. Inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance (Jones and Evans, 1997). Therefore, nitric oxide is contraindicated in stable COPD.
i- Narcotics (morphine):

Morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects (*Poole et al.*, 1998).

j- Others:

Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupuncture, homeopathy) cannot be recommended (*ATS/ERS 2004*).

Figure 4: Pharmacologic Therapy by Disease Severity (*GOLD 2016*):
### Table 5: Pharmacologic Therapy by Disease Severity *(GOLD 2016)*:

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Choice</th>
<th>Second Choice</th>
<th>Alternative Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Short acting anticholinergic</td>
<td>Long acting anticholinergic Or Long acting beta 2 agonist Or Short acting beta 2 agonist and short acting anticholinergic</td>
<td>Thyophylline</td>
</tr>
<tr>
<td></td>
<td>Or Short acting beta 2 agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Long acting anticholinergic Or</td>
<td>Long acting anticholinergic And Long acting beta 2 agonist</td>
<td>Short acting beta 2 agonist And / Or Short acting anticholinergic Thyophylline</td>
</tr>
<tr>
<td></td>
<td>Long acting beta 2 agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Inhaled corticosteroid +</td>
<td>Long acting anticholinergic and Long acting beta 2 agonist Or Long acting anticholinergic and phosphodiesterase-4 inhibitor Or Long acting beta 2 agonist and phosphodiesterase-4 inhibitor</td>
<td>Short acting beta 2 agonist And / Or Short acting anticholinergic Thyophylline</td>
</tr>
<tr>
<td></td>
<td>Long acting anticholinergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or Long acting beta 2 agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long acting beta 2 agonist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carbocysteine

Short acting beta 2 agonist
And / Or
Short acting anticholinergic

Thyophylline

<table>
<thead>
<tr>
<th>D</th>
<th>Inhaled corticosteroid + Long acting anticholinergic And/ Or Long acting beta 2 agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhaled corticosteroid + Long acting beta 2 agonist and Long acting anticholinergic</td>
</tr>
<tr>
<td></td>
<td>Or Inhaled corticosteroid + Long acting beta 2 agonist and Phosphodiesterase-4 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Or Long acting anticholinergic and Long acting beta 2 agonist</td>
</tr>
<tr>
<td></td>
<td>Or Long acting anticholinergic and Phosphodiesterase-4 inhibitor</td>
</tr>
</tbody>
</table>

B) Non- pharmacologic treatment:

1) Rehabilitation:

Pulmonary rehabilitation is a program of exercise, disease management and counseling coordinated to benefit the individual. Pulmonary rehabilitation has been shown to improve shortness of breath and exercise capacity. Pulmonary rehabilitation covers a range of non-pulmonary problems including exercise de-conditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. These problems have complex interrelationships and improvement in any one of these interlinked processes can interrupt the “vicious circle” in COPD (Fig. 2). A comprehensive statement on pulmonary rehabilitation has been prepared by the ATS/ERS (Nici et al., 2006).
The components of pulmonary rehabilitation program include exercise training, nutrition counseling, and education (Lacasse et al., 2002).

2) Oxygen Therapy:

One of the principal non pharmacologic treatments for patients with Stage IV: Very Severe COPD (ATS 1995).

The primary goal of oxygen therapy is to increase the baseline PaO2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO2 at least 90%, which will preserve vital organ function.

Long-term oxygen therapy is generally introduced in Stage IV:

Very Severe COPD for patients who have:
• PaO2 at or below 7.3 kPa (55 mm Hg) or SaO2 at or below 88%, with or without hypercapnia over three week period.

• PaO2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) over three week period.

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (Stoller et al., 2010).

Oxygen is usually delivered by:

• Facemask, with appropriate inspiratory flow rates varying between 24% and 35%.

• Nasal cannulae but requires additional blood gas monitoring.

• Fixed oxygen Concentrator with plastic piping allowing the patient to use oxygen in their living area and bedroom. Treatment should be for at least 15 hours per day and preferably longer (Currie and Douglas, 2007).

3) Ventilatory Support:

Noninvasive ventilation is now widely used to treat acute exacerbations of COPD (Lightowler et al., 2003) and with stable very severe COPD. The combination of NIV and long term oxygen consumption may be used in some patients with daytime hypercapnia and in COPD patients with obstructive sleep apnea (Marin et al., 2010).
4) Surgical Treatments:

**Bullectomy:**

Removal of a large bulla that does not contribute to gas exchange and decompresses the adjacent lung parenchyma. This procedure is effective in reducing dyspnea and improving lung function *(Mehran and Deslauriers, 1995)*.

Some investigators have recommended that the bulla must occupy 50% or more of the hemithorax and produce definite displacement of the adjacent lung before surgery is performed *(Laross et al., 1986)*.

**Lung volume reduction surgery (LVRS):**

Lung volume reduction surgery involves removal of segments of inefficient emphysematous lung parenchyma in order to promote better gas exchange in the remaining, less affected part *(Fishman et al., 2008)*.

LVRS reduces hyperinflation and improves muscle mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition) *(Criner et al., 1998)*.

In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates *(Fessler and Permutt, 1998)*.

Interest has been growing in bronchoscopic lung volume reduction in patients with COPD (BLVRS). This involves obstructing emphysematous areas of lung with, for example, an endobronchial valve, therefore avoiding the risks associated with major surgery *(Hopkinson et al., 2005)*.
Lung transplantation:

In patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (Christie et al., 2010).

Criteria for lung transplantation include: BODE index of 7-10 and at least one of the following: history of exacerbation associated with acute hypercapnia PaCO2 > 6.7 kPa (50 mm Hg), PaO2 < 7.3-8.0 kPa (55-60 mm Hg) and secondary pulmonary hypertension, FEV1 < 20% predicted, DLCO <20% predicted or homogenous distribution of emphysema (Orens et al., 2006).
Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Definition:

(Anthonisen et al., 1987) defined AECOPD clinically by the presence of one or more of the following findings:

1. Worsening of dyspnea.
2. Increase in sputum volume.
3. Increase in sputum purulence.

Classified it into:

- **Level I** (severe) has all the three symptoms.
- **Level II** (moderate) has two of them.
- **Level III** (mild) has one symptom plus at least one of the followings:
  
a. Upper respiratory infection in the past 5 days.
b. Fever without another apparent cause.
c. Increased wheezing.
d. Increased cough.
e. Increased respiratory rate > 25 breaths/minute.
f. Increased heart rate by 20% above baseline.

Rodriguez-Roisin (2000): proposed the following definition of AECOPD as “it is a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates change in regular medication in a patient with underlying COPD”.
He also proposed a staging classification system based on health care utilization:

**Mild:** patient has an increased need for medications, which can be managed in patient’s normal environment.

**Moderate:** patient has an increased need for medications and feels the need to seek additional medical assistance.

**Severe:** patient/care giver recognizes deterioration in condition requiring hospitalization.

**GOLD (2016):** An exacerbation of COPD is an acute event characterized by worsening of the patients respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications (Celli et al., 2007).

**Causes and risk factors of AECOPD:**

The most common causes of an exacerbation are infection of the tracheobronchial tree by virus (Rhinovirus spp., influenza); bacteria (Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Enterobacteriaceae spp., Pseudomonas spp.) and air pollution (White et al., 2003).

**Pathology of AECOPD:**

Although it has been assumed that exacerbations are associated with increased airway inflammation, there has been little information available on the nature of inflammatory markers, because of the difficulty in performing invasive maneuvers such as brushing, lavage or biopsies during an acute exacerbation of COPD. However, the technique of
sputum induction allows the study of these patients during exacerbations, and it has been shown that it is safe and well tolerated in COPD patients. There were more increase in neutrophils, T. lymphocytes (CD3+) and tumor necrosis factor-alpha- positive cells, while there were no changes in the number of CD4+ or CD8+ T cells, macrophages or mast cells (Wedzicha, 2002).

Pathogenesis of AECOPD:

Many exacerbations are infectious in origin (either bacterial or viral). However, many patients with COPD are colonized by bacteria when clinically stable. Thus, there are a substantial percentage of exacerbation episodes of unclear cause. Potential mechanisms include air pollution, changes in ambient temperature and pulmonary emboli, among others (smoking and cessation of medication) (Wedzicha, 2001).

Pathophysiology of AECOPD:

Airflow obstruction is almost unchanged during mild exacerbations and only slightly reduced during severe exacerbations (Seemungal et al., 2000). Severe exacerbations are accompanied by a significant worsening of pulmonary gas exchange (due mostly to increased ventilation-perfusion inequality) and, potentially, by respiratory muscle fatigue. Worsening ventilation-perfusion relationships in exacerbations of COPD are multifactorial and relate to airway inflammation and oedema, mucus hypersecretion and bronchoconstriction, which affects ventilation and causes hypoxic vasoconstriction of pulmonary arterioles, which reduces perfusion. Alveolar hypoventilation and respiratory muscle fatigue also contribute to hypoxaemia, hypercapnia and respiratory acidosis leading to severe respiratory failure and death. Hypoxia and respiratory acidosis
produce pulmonary vasoconstriction imposing an additional load on the right ventricle and, together with renal and hormonal changes, can result in peripheral oedema (Barbera et al., 1997).

**Diagnosis and assessment of severity:**

1-Clinically:

In 2004, the UK National Institute for Clinical Excellence (NICE) developed consensus statements. Stated the following:

a) **Symptoms of an exacerbation:**

Exacerbations of COPD can be associated with the following symptoms:

- Increased dyspnea.
- Increased sputum purulence.
- Increased sputum volume.
- Increased cough.
- Upper airway symptoms (e.g. colds and sore throats).
- Increased wheeze.
- Chest tightness.
- Reduced exercise tolerance.
- Fluid retention.
- Increased fatigue.
- Acute confusion.

- Chest pain and fever are uncommon features of COPD exacerbations and should prompt a search for other etiologies.

b) **Assessment of the severity of an exacerbation (signs of severity):**

Some exacerbations are mild and self-limiting. These are frequently managed by patients at home without consulting healthcare professionals. Other exacerbations are severe, carry a risk of death and require hospitalization. A number of factors can be used to assess the
Review of literature

severity of an exacerbation. Not all will be present, but the occurrence of any of these should alert the clinician as shown in table (6) (Celli et al., 2004).

Table (6): Clinical history, physical findings and diagnostic procedures in patients with exacerbation of chronic obstructive pulmonary disease (COPD) (Celli et al., 2004):

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbid conditions(1)</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>History of frequent exacerbations</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Severity of COPD</td>
<td>Mild/moderate</td>
<td>Moderate/Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodynamic evaluation</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable/unstable</td>
</tr>
<tr>
<td>Use accessory respiratory muscles, tachypnea</td>
<td>Not present</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Persistent symptoms after initial therapy</td>
<td>No</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic procedures</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood tests(2)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum drug concentrations(3)</td>
<td>If applicable</td>
<td>If applicable</td>
<td>If applicable</td>
</tr>
<tr>
<td>Sputum gram stain and culture</td>
<td>No(4)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

+: Unlikely to be present.  ++: likely to be present.

+++: very likely to be present.
(i) The more common co-morbid conditions associated with poor prognosis in exacerbations are congestive heart failure, coronary artery disease, diabetes mellitus, renal and liver failure.

(ii) Blood tests include cell blood count, serum electrolytes, renal and liver function.

(iii) Serum drug concentrations, consider if patients are using theophylline, warfarin, carbamezepine, digoxin.

(iv) Consider if patient has recently been on antibiotics.

Assessment of COPD exacerbations: signs of severity (GOLD., 2016)

- Use of accessory respiratory muscles.
- Paradoxical chest wall movements.
- Worsening or new onset central cyanosis.
- Development of peripheral oedema.
- Hemodynamic instability.
- Deteriorated mental status.
2- Laboratory:

a) Pulse oximetry and arterial blood gas measurement:

Can be used to evaluate a patient’s oxygen saturation and need for supplemental oxygen therapy. Moderate-to-severe acidosis (pH < 7.36) plus hypercapnia (PaCO2 > 6-8 kPa, 45-60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation (Celli et al., 2004).

b) Chest X-ray and ECG:

Chest radiographs both postero-anterior, laterally views are useful in identifying alternative diagnosis that can mimic the symptoms of an exacerbation (Pauwel et al., 2001).

An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes especially if a previously normal ECG is available (postma et al., 1999).

c) Spirometry and PEF:

Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended. In general, PEF < 100 L/min. or an FEV1 < 1 L indicates a sever exacerbation (Neiwoehner et al., 2000).

d) Bio-chemical tests:

Abnormalities can be associated with an exacerbation and include electrolyte disturbance (s) (e.g., hyperglycemia, hyponatremia,
hypokalemia), poor glucose control and metabolic acid-base disorder. *(Pauwel et al., 2001)*

Whole blood count: may identify polycythemia, anemia, or leukocytosis.

**Differential diagnosis of an exacerbation:**

Other conditions may present with similar symptoms in patients with COPD. These must be considered and excluded when making a diagnosis of an exacerbation, other causes of similar symptoms in patients with COPD are *(Currie and Wedzicha, 2007):*

- pneumonia
- pneumothorax
- left ventricular failure/pulmonary oedema
- pulmonary embolus
- lung cancer
- upper airway obstruction
- pleural effusion
- Recurrent aspiration.
Treatment:

1) HOME MANAGEMENT:

![Algorithm for the Management of an Exacerbation of COPD at Home](Rodriguez-Roisin, 2006)

**Figure 6**: Algorithm for the Management of an Exacerbation of COPD at Home (*Rodriguez-Roisin, 2006*)

**Home management includes:**

a) **Patient education:**

By checking inhalation technique and consider use of spacer devices (*ATS/ERS, 2004*).
b) Bronchodilators:

Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short acting bronchodilator therapy including short-acting β2-agonist (albuterol, salbutamol, terbutaline) and/or ipratropium MDI with spacer or hand-held nebuliser as needed, also consider adding long-acting bronchodilator if patient is not using it (National Institute for Clinical Excellence., 2010).

c) Corticosteroids:

Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV1) and hypoxemia (PaO2) (Davies et al., 1999). A dose of 30–40 mg prednisone per day for 5 days (Leuppi et al., 2013) in addition to use inhaled corticosteroid (Maltais et al., 2004).

d) Antibiotics:

May be initiated in patients moderate to severe ill with exacerbations and altered sputum characteristics (Ram et al., 2006). There choice should be based on local bacteria resistance patterns. Including the use of amoxicillin/ampicillin, cephalosporins (cefpodoxime, cefprozil), doxycycline (Adams and Anzueto, 2000) and macrolides (azithromycin, clarithromycin) (Swanson et al., 2002). If the patient has failed prior antibiotic therapy consider: amoxicillin/clavulanate moxifloxacin) (Wilson et al., 2002). Procalcitonin 3 , a marker that is specific for bacterial infection, may be of value in the decision to use antibiotics (Christ-Crain et al., 2004).
Indication of antibiotic use: (Woodhead et al., 2005)

patient have the three cardinal symptoms, patient have two cardinal symptoms and increased sputum pulance is one of them, patient requiring mechanical ventilation (invasive or non invasive).

The recommended length of antibiotic therapy is 5-10 days.

e) Mucolytics:

There is no evidence of shortening in the duration of the exacerbations or improvement of the FEV1 values when using mucolytics in AECOPD. In the non acute COPD setting, systematic reviews have found a reduction in the number of acute exacerbation and days of illness when mucolytics were routinely used (Poole and Black, 2001).

f) Anticoagulants:

Subcutaneous heparin administration could be of promising beneficial therapeutic value in exacerbated COPD patients due to increased incidence of DVT and pulmonary embolism. (Rizkallah et al., 2009).

g) Diuretics:

Diuretics are indicated if there is peripheral oedema and a raised jugular venous pressure (BTS, 1997).

2) HOSPITAL MANAGEMENT:

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support (Connors et al., 1996).
Indications for Hospital Assessment or Admission for Exacerbations of COPD (GOLD 2016):

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea.
- Severe underlying COPD.
- Onset of new physical signs (e.g., cyanosis, peripheral edema).
- Failure of exacerbation to respond to initial medical management.
- Significant comorbidities.
- Frequent exacerbations.
- Newly occurring arrhythmias.
- Older age.
- Insufficient home support.

Treatment for hospitalized patient:

a) Bronchodilators:

Short acting β2 agonist (Albuterol, salbutamol) and/or Ipratropium MDI with spacer or hand-held nebuliser as needed (Turner et al., 1997)

b) Supplemental oxygen (if saturation <90 %): 

Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient’s hypoxemia with a target saturation of 88-92% (Austin et al., 2010). Adequate levels of oxygenation (PaO2 > 8.0 kPa, 60 mm Hg, or SaO2 > 90%) are easy to achieve in uncomplicated exacerbations, but CO2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without CO2 retention or
acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient (Celli et al., 2004).

c) Corticosteroids:

If not contraindicated, prednisone 30–40 mg per day for 10-14 days unless the patient cannot tolerate oral intake, equivalent dose intravenous for up to 14 days (O’Donnell et al., 2007) and also consider the use of inhaled corticosteroids by MDI or hand-held nebulizer (Maltais et al., 2004).

d) Antibiotics (based on local bacteria resistance patterns):

May be initiated in patients that have a change in their sputum characteristics (purulence and/or volume) . The Choice of antibiotics should be based on local bacteria resistance patterns such as Amoxicillin/clavulanate (Anzueto et al., 2001) and respiratory fluoroquinolones (gatifloxacín, levofloxacín, moxifloxacín) (Gotfried et al., 2001). If Pseudomonas spp. and/or other Enterobacteracíes spp. are suspected, consider combination therapy (ATS/ERS, 2004).

Discharge criteria from hospital: (GOLD 2016):

- Able to use long acting bronchodilator.
- Inhaled short acting beta 2 agonists is required no more than every 4 hrs.
- Patient is able to walk across room.
- Patient is able to eat and sleep without awakening by dyspnea.
- Patient has been clinically stable for 12-24 hrs.
- Arterial blood gases have been stable for 12-24 hrs.
- Patient fully understands correct use of medications.
Indications for ICU Admission of Patients with Exacerbations of COPD (GOLD 2016)

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia (PaO2 < 5.3 kPa, 40 mmHg), and/or severe/worsening hypercapnia (PaCO2 > 8.0 kPa, 60 mmHg), and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability need for vasopressors.

Treatment in patients requiring ICU (Celli et al., 2004):

a) Supplemental oxygen

b) Ventilatory support

The primary objectives of mechanical ventilatory support in patients with COPD exacerbations are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive intermittent ventilation (by nasal or facial mask) and invasive (conventional) mechanical ventilation by oro-tracheal tube or tracheostomy (GOLD, 2016).

Noninvasive positive pressure ventilation (NPPV) should be offered to patients with exacerbations when, after optimal medical therapy and oxygenation, respiratory acidosis (pH ≤ 7.35) and/or (PaCO2 ≥ 6.0 KPa, 45 mmHg), severe dysnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of
respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.

If pH < 7.30, NPPV should be delivered under controlled environments such as intermediate intensive care units (ICUs) and/or high-dependency units.

If pH < 7.25, NPPV should be administered in the ICU and intubation should be readily available.

c) Bronchodilators

- Short acting β2 agonist (Albuterol, salbutamol) and ipratropium MDI with spacer, two puffs every 2–4 h.
- If the patient is on the ventilator, consider MDI administration.
- Consider long-acting β agonist.

d) Corticosteroids

- If patient tolerates oral medications, prednisone 30–40 mg per day for 10 days.
- If patient cannot tolerate, give the equivalent dose I.V. for up 14 days.
- Consider use inhaled corticosteroids by MDI or hand-held nebuliser.

e) Antibiotics

- Choice should be based on local bacteria resistance pattern.
- Amoxicillin/clavulanate.
• Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin).
• If Pseudomonas spp. and or other Enterobacteraceae spp. are suspected consider combination therapy

Indications for invasive mechanical ventilation (GOLD 2016):

• Unable to tolerate NIV or NIV failure.
• Respiratory or cardiac arrest.
• Respiratory pauses with loss of consciousness or gasping for air.
• Diminished consciousness, psychomotor agitation inadequately controlled by sedation.
• Massive aspiration.
• Persistant inability to remove respiratory secretions.
• Heart rate < 50 b/min with loss of alertness.
• Severe hemodynamic instability without response to fluids and vasoactive drugs.
• Severe ventricular arrhythmia.
• Life-threatening hypoxemia.

Hazards of IMV: ventilator acquired pneumonia, barotrauma, and failure of weaning.

Weaning from mechanical ventilation: sheft to NIV facilitate weaning, prevents reintubation, and reduces mortality (International Consensus Conference in intensive care medicine 2001). Use of pressure support or a T-piece also facilitate weaning (Ferrer et al., 2009).
Erythropoietin Hormone

- **Definition:**

  *Erythropoietin* also known as EPO, is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa. Also called hematopoietin or hemopoietin. *(The American Heritage® Stedman's Medical Dictionary., 2004).*

- **History:**

  In 1905, Paul Carnot, a professor of medicine in Paris, and his assistant, Clotilde Deflandre, proposed the idea that hormones regulate the production of red blood cells. After conducting experiments on rabbits subject to bloodletting, Carnot and Deflandre attributed an increase in red blood cells in rabbit subjects to a hemotropic factor called hemopoietin. Eva Bonsdorff and Eeva Jalavisto continued to study red cell production and later called the hemopoietic substance 'erythropoietin'. Further studies investigating the existence of EPO by K.R. Reissman (unknown location) and Allan J. Erslev (Thomas Jefferson Medical College) demonstrated that a certain substance, circulated in the blood, is able to stimulate red blood cell production and increase hematocrit. This substance was finally purified and confirmed as erythropoietin, opening doors to therapeutic uses for EPO in diseases such as anemia. *(Ahmet Höke 2005).*

  Haematologist John Adamson and nephrologist Joseph W. Eschbach looked at various forms of renal failure and the role of the
natural hormone EPO in the formation of red blood cells. Studying sheep and other animals in the 1970s, the two scientists helped establish that EPO stimulates the production of red cells in bone marrow and could lead to a treatment for anemia in humans. In 1968, Goldwasser and Kung began work to purify human EPO, and managed to purify milligram quantities of over 95% pure material by 1977 (Miyake et al., 1997). Pure EPO allowed the amino acid sequence to be partially identified and the gene to be isolated. Later, an NIH-funded researcher at Columbia University discovered a way to synthesize EPO. Columbia University patented the technique, and licensed it to Amgen. Controversy has ensued over the fairness of the rewards that Amgen reaped from NIH-funded work, and Goldwasser was never financially rewarded for his work (Angell et al., 2005).

In the 1980s, Adamson, Joseph W. Eschbach, Joan C. Egrie, Michael R. Downing and Jeffrey K. Browne conducted a clinical trial at the Northwest Kidney Centers for a synthetic form of the hormone, Epogen, produced by Amgen. The trial was successful, and the results were published in the New England Journal of Medicine in January 1987 (Eschbach et al., 1987). In 1985, Lin et al isolated the human erythropoietin gene from a genomic phage library and were able to characterize it for research and production (Suggs et al., 1985). Their research demonstrated the gene for erythropoietin encoded the production of EPO in mammalian cells that is biologically active in vitro and in vivo. The industrial production of recombinant human erythropoietin (RhEpo) for treating anemia patients would begin soon after.

In 1989, the US Food and Drug Administration approved the hormone Epogen, which remains in use today.
• Synthesis:

It is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. It is also produced in perisinusoidal cells in the liver. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood. In addition to erythropoiesis, erythropoietin also has other known biological functions. For example, it plays an important role in the brain's response to neuronal injury (Sirén et al., 2001). EPO is also involved in the wound healing process (Haroon et al., 2003).

Erythropoietin levels in blood are quite low in the absence of anemia, at around 10 mU/ml. However, in hypoxic stress, EPO production may increase 1000-fold, reaching 10,000 mU/ml of blood. EPO is produced mainly by interstitial cells in the peritubular capillary bed of the renal cortex. It is synthesized by renal peritubular cells in adults, with a small amount being produced in the liver (Fisher et al., 1996). Regulation is believed to rely on a feedback mechanism measuring blood oxygenation. Constitutively synthesized transcription factors for EPO, known as hypoxia-inducible factors, are hydroxylated and proteosomally digested in the presence of oxygen (Jelkmann et al., 2007).

Several compounds have been identified that can be taken orally to stimulate endogenous EPO production. Most of the compounds stabilize the hypoxia-inducible transcription factors which activate the EPO gene. The compounds include oxo-glutarate competitors, but also simple ions such as cobalt (II) chloride (Jelkmann et al., 2012). Inhalation of a xenon/oxygen mixture activates production of the transcription factor HIF-1-alpha, which leads to increased production of erythropoietin.
and improved performance. It has been used for this purpose in Russia since at least 2004.

**Exogenous erythropoietin** is produced by recombinant DNA technology in cell culture. Several different pharmaceutical agents are available with a variety of glycosylation patterns, and are collectively called erythropoiesis-stimulating agents (ESA). The specific details for labelled use vary between the package inserts, but ESAs have been used in the treatment of anemia in chronic kidney disease, anemia in myelodysplasia, and in anemia from cancer chemotherapy. Boxed warnings include a risk of death, myocardial infarction, stroke, venous thromboembolism, and tumor recurrence.

Exogenous erythropoietin has been used illicitly as a performance-enhancing drug, it can often be detected in blood, due to slight differences from the endogenous protein, for example, in features of post translational modification.

- **Medical uses:**

Erythropoietins available for use as therapeutic agents are produced by recombinant DNA technology in cell culture, and include Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa), they are used in treating anemia resulting from chronic kidney disease, inflammatory bowel disease (Crohn's disease and ulcer colitis) and myelodysplasia from the treatment of cancer (chemotherapy and radiation) (Liu et al., 2013).

The package inserts include boxed warnings of increased risk of death, myocardial infarction, stroke, venous thromboembolism, and tumor
recurrence, particularly when used to increase the hemoglobin levels to more than 11 to 12 g/dl.

Table (7): Available forms:

- Recombinant erythropoietin has a variety of glycosylation patterns giving rise to alpha, beta, delta, and omega forms:
  - Epopeitin Alfa:
    - Darbepoetin (Aranesp)
    - Epeopt (Lupin pharma)
    - Nanokine (Nanogen Pharmaceutical biotechnology, Vietnam)
    - Epofit (Intas pharma)
    - Epogen, made by Amgen
    - Epopin
    - Eprex, made by Janssen-Cilag
    - Binocrit, made by Sandoz
    - Procrit
  - Epopeitin Beta:
    - NeoRecorum, made by Hoffmann–La Roche
    - Recormon
    - Methoxy polyethylene glycol-epoetin beta (Mircera) by Roche

- Epoetin Zeta (biosimilar forms for epoetin alpha):
  - Silapo (Stada)
  - Retacrit (Hospira)

- Miscellaneous:
  - Epeopt, made by Lupin Pharmaceuticals
  - EPOTrust, made by Panacea Biotec Ltd
  - Erypro Safe, made by Biocon Ltd.
  - Repoitin, made by Serum Institute of India Limited
  - Vintor, made by Emcure Pharmaceuticals
  - Epoft, made by Intas pharma
  - Erykine, made by Intas Biopharmaceutica
  - Wepox, made by Wockhardt Biotech
### Review of literature

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<th>Epoetin Delta:</th>
<th>Epoetin Omega:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Dynepo trademark name for an erythropoiesis stimulating protein, by Shire plc</td>
<td>o Epomax</td>
</tr>
<tr>
<td>o Epoetin Omega:</td>
<td>o Espogen, made by LG life sciences.</td>
</tr>
<tr>
<td>o Epomax</td>
<td>o ReliPoietin, made by Reliance Life Sciences</td>
</tr>
<tr>
<td>o Epoetin Omega:</td>
<td>o Shanpoietin, made by Shantha Biotechnics Ltd</td>
</tr>
<tr>
<td>o Epomax</td>
<td>o Zyrop, made by Cadila Healthcare Ltd.</td>
</tr>
<tr>
<td>o EPIAO (rHuEPO), made by Shenyang Sunshine Pharmaceutical Co., LTD. China</td>
<td>o EPIAO (rHuEPO), made by Shenyang Sunshine Pharmaceutical Co., LTD. China</td>
</tr>
<tr>
<td>o Cinnapoietin, made by CinnaGen biopharmaceutical Iran.</td>
<td>o Cinnapoietin, made by CinnaGen biopharmaceutical Iran.</td>
</tr>
</tbody>
</table>

Darbepoetin alfa, which early literature during its development often termed as novel erythropoiesis-stimulating protein (NESP), is a form created by five substitutions (Asn-57, Thr-59, Val-114, Asn-115 and Thr-117) that create two new N-glycosylation sites. This glycoprotein has a longer terminal half-life, meaning it may be possible to administer it less frequently (Macdougall, 2000).
• **Function:**

1) **Red blood cell production:**

The primary role of erythropoietin is an essential hormone for red cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells by targeting CFU-E, proerythroblast and basophilic erythroblast subsets in the differentiation. Erythropoietin has its primary effect on red blood cell progenitors and precursors (which are found in the bone marrow in humans) by promoting their survival through protecting these cells from apoptosis. Erythropoietin is the primary erythropoietic factor that cooperates with various other growth factors (e.g., IL-3, IL-6, glucocorticoids, and SCF) involved in the development of erythroid lineage from multipotent progenitors. The burst-forming unit-erythroid (BFU-E) cells start erythropoietin receptor expression and are sensitive to erythropoietin. Subsequent stage, the colony-forming unit-erythroid (CFU-E), expresses maximal erythropoietin receptor density and is completely dependent on erythropoietin for further differentiation. Precursors of red cells, the proerythroblasts and basophilic erythroblasts also express erythropoietin receptor and are therefore affected by it.

2) **Non hematopoietic roles:**

Erythropoietin has a range of actions including vasoconstriction-dependent hypertension, stimulating angiogenesis, and inducing proliferation of smooth muscle fibers. It can increase iron absorption by suppressing the hormone hepcidin (**Ashby et al., 2010**).
EPO levels of 100 times the baseline have been detected in brain tissue as a natural response to hypoxic damage (Marti et al., 1997).

In rats, pretreatment with erythropoietin was associated with neuronal protection during induced cerebral hypoxia. Trials in humans have not been reported (Sirén et al., 2001).

Multiple studies have suggested that EPO improves memory. This effect is independent of its effect on hematocrit. Rather, it is associated with an increase in hippocampal response and effects on synaptic connectivity, neuronal plasticity, and memory-related neural networks. EPO may have effects on mood (Miskowiak et al., 2007).

- **Mechanism of action:**

  Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EpoR) (Middleton et al., 1999).

  EPO is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. EPO's half-life may vary between endogenous and various recombinant versions. Additional glycosylation or other alterations of EPO via recombinant technology have led to the increase of EPO's stability in blood (thus requiring less frequent injections). EPO binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signaling cascade. Erythropoietin receptor expression is found in a number of tissues, such as bone marrow and peripheral/central nervous tissue. In the blood stream, red cells themselves do not express erythropoietin receptor, so cannot respond to EPO. However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neocytolysis (Spivak et al., 1986).
Erythropoietin hormone and COPD

COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years, and die prematurely from it or its complications (GOLD., 2016). It was estimated that 6% of the adult population were diagnosed as having COPD. COPD was estimated to become the third leading cause of death and fifth cause of disability by the year 2020 (Weiss et al., 2005). COPD might be considered a disorder associated with extrapulmonary effects caused by comorbidities that are either secondary to inflammatory burden of COPD or occurring in association with COPD due to sharing of same risk factors (Fabbri et al., 2008).

It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD (Wedzicha et al., 1983). However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis (Attaran et al., 2009).

Several hypotheses were proposed for this finding: for example it was thought that the inflammatory burden of COPD caused anemia of chronic disorders due to the effects of IL-1 and TNF-α (anemia in COPD), also CRP and IL-6 (John et al., 2005). This might occur through shortened RBC survival, iron homeostasis dysregulation and impaired bone marrow erythropoietic response. Nutritional derangements in COPD patients were proposed as a cause for anemia (Varraso et al., 2008). Also, tobacco smoking and its role in oxidative stress has a role in RBCs production (Calverley et al., 1982). Lastly, the role of comorbidities frequently encountered in COPD patients as upper GI bleeding and folate deficiency was proposed however they were largely related to smoking.
EPO is an endogenous glycoprotein hormone that serves as the primary stimulus for erythropoiesis. The kidney is the primary site of EPO production, but the liver also produces the hormone. EPO acts in the bone marrow, where it promotes terminal differentiation of progenitor cells into erythrocytes (Erslev et al., 1991).

Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase (Jelkmann et al., 1992). Ninety percent of EPO is produced in the peritubular cells of the adult kidney in response to a decrease in tissue oxygenation. There is evidence indicating that the protein on these cells which detects oxygen saturation of the blood is a heme-containing moiety. As the pO2 of the plasma, a function of the hematocrit decreases, EPO concentration will increase (Erslev et al., 1980).

The hematocrit is one of the most precise methods of determining the degree of anemia or polycythemia (excessive amount of red blood cells). The hematocrit represents the volume of red blood cells in 100 ml of blood and is therefore reported as a percentage (Greenleaf et al., 1979).

Anemia is not a disease, but a term indicating insufficient hemoglobin to deliver oxygen to the cells. It is always a secondary phenomenon. Optimum values in an adult male are: Hemoglobin 14–18 gm/dL and hematocrit 40.0% to 54.0% (Billett et al., 1990).

There is a debate about the changes which occur in erythropoiesis in response to COPD. Some patients have anemia and others have
Review of literature

polycythemia, thus the study was performed to assess the changes in erythropoietin in COPD patients in different stages.

There are two factors which cause increased production of EPO hormone in COPD patients which include hypoxia and anemia in COPD patients.

- **Hypoxic regulation of erythropoiesis**:

  The relationship between the O2 content of the blood and erythropoiesis was first described by the French anatomist Francois-Gilbert Viault in 1890 (*Viault et al., 1890*), who observed a rise in RBC numbers on a journey to the highlands of Peru (Morococha, about 4500 m). Indeed, the specific stimulus for Epo expression is a fall in tissue O2 pressure (PO2). Epo production increases under hypoxic conditions in the kidneys and, in minor amounts, in distinct other organs such as the liver and the brain.

  The human haematopoietic Epo receptor (Epo-R) is a 484 amino acid glycoprotein of about 60 kDa, which belongs to the cytokine class I receptor family and forms homodimers. On the binding of Epo to the Epo-R dimer, cytoplasmic Janus kinases 2 (JAK2) catalyse the phosphorylation of tyrosine residues of the Epo-R and of various intracellular proteins enzymes and (transcription factors). Erythropoiesis is a slow-acting process. Following a rise in plasma Epo it takes 3–4 days before reticulocytosis becomes apparent.

  **Molecular mechanism of the hypoxia-induced Epo expression**:  

  The mechanisms of the renal and the hepatic Epo expression differ. (i) Renal cells respond in an all-or-nothing fashion to hypoxia (*Koury et
Review of literature

al., 1989), whereas hepatoma cells respond in a graded way. (ii) The hypoxia-response elements (HREs) in control of the Epo gene are located upstream in the kidney (between 9.5 and 14 kb 5' to Epo) but downstream in the liver (within 0.7 kb 3' to Epo) according to studies in transgenic mice (Kochling et al., 1998). In both tissues Epo expression is under the control of distinct transcription factors. The Epo promoter is suppressed by GATA-2 in normoxia (Tsuchiya et al., 1997). GATA-2 levels decrease in hypoxia. More importantly the Epo enhancer is activated by hypoxia-inducible transcription factors (HIFs). These are composed of an O2-labile α-subunit (120 kDa; isoforms 1α , 2α or 3α ) and a constitutive β-subunit (90–95 kDa). Although the prototype HIF-1 was discovered in studies of Epo (Wang & Semenza, 1995), later investigations have identified HIF-2 (also called EPAS1 for endothelial PAS domain protein 1) as the primary transcription factor inducing Epo expression (Warnecke et al., 2004). HIF-2α is activated by the stress-responsive deacetylase Sirtuin 1 (Dioum et al., 2009).

The C-terminus of the HIF-α subunits comprises O2-dependent degradation domains (O-DDD) that are prolyl hydroxylated in the presence of O2 (Epstein et al., 2001). The prolyl hydroxylated HIF-α combines with von Hippel-Lindau tumour suppressor protein (VHL)/E3 ligase and promptly undergoes proteasomal degradation (Pugh et al., 1997). As PHD-2 and PHD-3 are themselves HIF-target genes, their expression increases and HIF-α levels decline during long-term hypoxic periods (Del Peso et al., 2003). This feedback regulation may explain the declining Epo production during chronic anaemia or prolonged stay at high altitude. Furthermore, the transcriptional activity of the HIFs is suppressed by HIF-α asparaginyl hydroxylation which prevents the
binding of the transcriptional co-activator CBP/p300. This reaction is catalysed by the factor inhibiting HIF-1 (Mahon et al., 2001).

The basal plasma concentration of Epo ranges from 6 to 32 IU/L. The plasma Epo concentration increases exponentially when Hb falls below \(\sim 12.5\) g/dl in humans not suffering from renal disease or inflammation. The response is dynamic with initially very high Epo values that drop towards the normal ones before [Hb] normalises. The mechanism of the rapid decrease is not fully understood, but it may in part be caused by lowered HIF-\(\alpha\) levels during long-term hypoxia (Stiehl et al., 2006).

Because Epo production depends on the tissue PO2, Epo expression is also activated when the arterial PO2 declines or when the O2-affinity of the blood increases. On ascent to altitude, Epo levels reach peak values after 1–2 days and then fall to a new plateau at about twice that present at sea-level (Abbrecht & Littell, 1972). As noted above HIF-\(\alpha\) levels decline during long-term hypoxic periods. In addition, the decrease in Epo production at continued hypoxia may be associated with the decrease in O2-affinity of the blood resulting from an increase in the intra erythrocytic concentration of 2,3-bisphosphoglycerate (Klausen, 1998).

- **Extra-renal sites affecting renal Epo production:**

  One hypothesis suggests that the brain modulates O2-dependent Epo expression in the kidney. Local hypoxia of the brain stem was associated with an increase in renal Epo production in experimental animals (von Wussow et al., 2005). Both astrocytes and neurons express Epo. Moreover, evidence suggests that glial cells contribute to circulating
Epo following the induction of hypoxia (Weidemann et al., 2009). Renal (but not hepatic) Epo mRNA levels are suppressed in transgenic mice lacking VHL or both VHL and HIF-1α in astrocytes (Weidemann et al., 2009). The mechanism by which astrocytes influence renal Epo expression still needs to be explored.

In addition the O2 supply to the skin has been implicated in the control of renal Epo expression (Boutin et al., 2008). According to this concept, an increased blood flow to the skin causes a reduction in the renal O2 supply. Mice with an epidermal deletion of VHL have increased Epo synthesis and develop erythrocytosis (Boutin et al., 2008). However, the concept of the dermal control of renal Epo production is not generally accepted (Paus et al., 2009), amongst other things because blood flow is not a major parameter in renal Epo synthesis. Also, dermal blood flow depends on body heat, which has not been shown to affect Epo production. Note, here, that renal nerve inputs appear to be less relevant for O2-dependent Epo expression in the kidney (Eckardt et al., 1992). Frankly speaking, the evidence assigning extra-renal sites a major role in the control of renal Epo production is far from convincing.
SUBJECTS AND METHODS

- **Study design:** prospective case control study.
- **Subjects:**
  
  This study was created on 50 subjects, 40 COPD patients with acute exacerbation from those attending the Chest Department at Banha University Hospitals in the period between December 2014 and December 2015 plus 10 age matched apparently healthy control subjects. They were divided into 2 groups:

  **Group 1:** 40 patients with COPD, Erythropoietin (EPO) hormone will be measured during exacerbation and after remission.

  **Group 2:** 10 apparently healthy subjects.

- **Inclusion criteria:**

  Patients with COPD diagnosed according to **GOLD (2016)** criteria.

- **Exclusion criteria:** Patients with history of:

  1. Bronchial asthma.
  2. Malignancy.
  3. Haematologic disorder.
  4. Systematic or autoimmune disorder.
  5. Thyroid disease.
  7. Heart failure (Ejection fraction <55%).
  8. Gastrointestinal or other hemorrhage.
  10. History of blood transfusion in the last 4 months.
Subjects and Methods

All subjects were submitted to the following:

1. **History taking:**
   - History of smoking (current, Ex. and non-smoking).
   - History of chest symptoms (cough, expectoration, dyspnea and wheeze).
   - History of any other comorbidities that may raise the erythropoietin hormone as bronchial asthma, malignancy or haematologic disorder, systematic or autoimmune disorder, thyroid disease, liver cirrhosis, heart failure (ejection fraction <55%), gastrointestinal or other hemorrhage, renal failure and history of blood transfusion in the last 4 months.

2. **Clinical examination:** both general and local examination.

3. **Radiological examination:** Plain chest x ray postero-anterior and lateral views.

4. **Pulmonary function tests (spirometry)** before and after bronchodilatation. Ambient temperature and pressure were entered with the patient data (age in years, weight in kilograms, height in centimeters and sex) so that all results were calculated as percent of predicted (% predicted) except for FEV₁/FVC.
   Pulmonary function tests were done using Spirolab.

   - Spirometry (F/V loop):

   1) **Maneuver of flow volume loop (Coates, 1988):**
      
      a. Calibration of the system was done.
      b. Explaining the procedure to the patient.
      c. The nose was clipped by nose clip and the patient was connected to the mouth piece.
d. The patient was instructed to breath tidally for several times then to inhale slowly till TLC was reached, then to exhale forcibly as much as he can so that the tracing crosses the red dotted 6 second line and RV was reached, then the patient was instructed to inhale forcibly till TLC.

e. This procedure was repeated three times and the best result was taken.

**From the flow volume loop, the following data were collected:**

- Forced vital capacity (FVC).
- Forced expiratory volume in the first second (FEV1).
- Forced expiratory volume in the first second to the forced vital capacity percent (FEV1/FVC %).
- Peak inspiratory and expiratory flow rate were read directly from the F-V loop.
- Forced expiratory flow at 75%, 50% and 25% of FVC were reported as the FEF\textsubscript{75%}, FEF\textsubscript{50}, FEF\textsubscript{25%} respectively with the subscripts referring to the percentage of FVC already exhaled *(Gregg, 1998).*

Every patient performed 3 successive trials pre-bronchodilator; the one with the best performance was chosen. Also every patient performed the test three successive times 15 minutes post-bronchodilator to determine the reversibility of airway obstruction. Inhaled bronchodilator given by metered dose inhaler (MDI). B\textsubscript{2}-adrenergic aerosol (Salbutamol 200 µg) was used because it has a rapid onset of action, usually within 5 minutes *(Miller et al., 2005).*

COPD Patients were classified according to their post-bronchodilator FEV1 into mild (FEV1 ≥80% and FEV1/FVC < 70 %
5- Erythropoietin hormone measurement:

- **Sample:**
The determination of EPO should be performed on human serum by ELISA.
Three cm of whole blood without adding any anticoagulant was collected in the morning between 7:30 a.m. to 12:00 noon, because diurnal variation of erythropoietin has been reported (Wide et al., 1989). Allow blood to clot between 2 and 8°C. Then, the serum should be promptly separated, preferably in a refrigerated centrifuge, and stored at -15°C or lower. Serum samples frozen at -15°C are stable for up to 12 month (Glory bioscience).

- **Principle of the procedure:**
The test is for the quantitative level of EPO in the sample, adopt purified Human EPO to coat microtiter plate, make solid-phase antibody, then add EPO to wells, Combine EPO antibody with labeled HRP to form antibody-antigen-enzyme-antibody complex, after washing completely, add TMB substrat solution, TMB substrate becomes blue color at HRP enzyme-catalyzed, reaction is terminated by the addition of a stop solution and the color change is measured at a wavelength of 450 nm. The concentration of EPO in the samples is then determined by comparing the O.D. of the samples to the standard curve.

- **Calculation of results:**
Take the standard concentration as the horizontal, the OD value for the vertical, draw the standard curve on graph paper, Find out the
corresponding concentration according to the sample OD value by the Sample curve, multiplied by the dilution multiple, or calculate the straight line regression equation of the standard curve with the standard concentration and the OD value, with the sample OD value in the equation, calculate the sample concentration, multiplied by the dilution factor, the result is the sample actual concentration.

- **Interpretation of results:**

  1. The standard curve is drawn under ideal conditions, and is just for reference rather than the actual standard curve diagram of the kit.

  2. It is advisable to establish proper assay data and standard curve according to respective laboratory conditions.

- **Range of EPO in healthy individuals:**

  (0 – 19) mU/ml (milliunits per milliliter) (*Kaushansky et al., 2016*).

6- **Routine investigations as:** Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar.

7- **Measuring the oxygen saturation** in the blood by pulse oximetry.

The results were tabulated and statistically analyzed.
Statistical Analysis

(Yadolah, 2003)

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, analysis of variance [ANOVA] test and chi-square test by SPSSV.11.

(1) Mean value $[\bar{X}]$

The sum of all observations divided by the number of observation:

$$\bar{X} = \frac{\sum X}{N}$$

Where $\sum X =$ sum of all list & $N =$ number of observations.

(2) Standard Deviation [SD]:

It measures the degree of scatter of individual varieties around their mean:

$$SD = \sqrt{\frac{E x^2 - (E x)^2}{N - 1}}$$

(3) Analysis of variance [ANOVA] tests:

According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.
(4) Chi-square:

The hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood ratio chi-square. Fisher's exact test and Yates' corrected chi-square were computed for 2x2 tables.

(5) Linear Correlation Coefficient [r]:

\[ r = \frac{\sum (X - \bar{X})(y - \bar{y})}{\sqrt{\sum (X - \bar{x})^2 \sum (y - \bar{y})^2}} \]

Where:
- \( X \) = independent variable.
- \( Y \) = Dependant variable.
RESULTS

Table (1) : Demographic data of control group.

<table>
<thead>
<tr>
<th>Sex</th>
<th>n&amp;%</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years ± SD</td>
<td>46 – 61</td>
<td>53.0 ± 6.57</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Demographic data of case group.

<table>
<thead>
<tr>
<th>Sex</th>
<th>n&amp;%</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33 (82.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (17.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years ± SD</td>
<td>47 – 61</td>
<td>54.88 ± 7.48</td>
<td></td>
</tr>
</tbody>
</table>

Table (3) : Pulmonary function tests of control group:

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC %</td>
<td>47 – 75</td>
<td>61.1 ± 14.18</td>
</tr>
<tr>
<td>Absolute FVC in liters</td>
<td>1.39 -- 2.05</td>
<td>1.72 ± 0.33</td>
</tr>
<tr>
<td>FEV1 %</td>
<td>47 – 79</td>
<td>63.7 ± 16.84</td>
</tr>
<tr>
<td>Absolute FEV1 in liters</td>
<td>1.3 -- 1.98</td>
<td>1.64 ± 0.34</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>80 – 101</td>
<td>90.5 ± 10.75</td>
</tr>
</tbody>
</table>
Table (4) : Pulmonary function tests of case group :

<table>
<thead>
<tr>
<th>Items</th>
<th>Pre bronchodilator</th>
<th>Post bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>40 patients</td>
<td>40 patients</td>
</tr>
<tr>
<td>Absolute FVC predicted in liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3 - 4.9</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.98 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>Absolute FVC in liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1.03 – 3.3</td>
<td>1 – 3.33</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.03 ± 0.61</td>
<td>2.1 ± 0.67</td>
</tr>
<tr>
<td>FVC % of Predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>30 – 71</td>
<td>22 – 73</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.2 ± 11.94</td>
<td>49.83 ± 13.45</td>
</tr>
<tr>
<td>Absolute FEV1 predicted in liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2 – 3.69</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.93 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>Absolute FEV1 in liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.3 – 2.01</td>
<td>0.32 – 2.15</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.18 ± 0.53</td>
<td>1.17 ± 0.52</td>
</tr>
<tr>
<td>FEV1 % of Predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>17 – 81</td>
<td>17 – 82</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>39.9 ± 18.17</td>
<td>40.08 ± 19.33</td>
</tr>
<tr>
<td>Percent of Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0 – 9.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.35 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>26 – 69</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54.25 ± 12.83</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I: Mild</td>
<td>4 (10.0 %)</td>
<td></td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Stage IV: Very Severe</td>
<td>16 (40.0%)</td>
<td></td>
</tr>
</tbody>
</table>
Results

**Figure (1):** Grading of COPD patients according to their pulmonary function tests

![Grading of COPD](image)

- Stage I: Mild
- Stage II: Moderate
- Stage III: Severe
- Stage IV: Very Severe
**Results**

**Table (5):** Comparison of pulmonary function tests between cases and control group.

<table>
<thead>
<tr>
<th></th>
<th>Case group mean ± SD</th>
<th>Control group mean ± SD</th>
<th>St t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC pre%</td>
<td>48.2 ± 11.94</td>
<td>61.1 ± 14.18</td>
<td>2.95</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Absolute FVC Pre in liters</td>
<td>2.03 ± 0.61</td>
<td>1.72 ± 0.33</td>
<td>1.58</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>FEV1 pre%</td>
<td>39.9 ± 18.17</td>
<td>63.7 ± 16.84</td>
<td>3.76</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Absolute FEV1 Pre in liters</td>
<td>1.18 ± 0.53</td>
<td>1.64 ± 0.34</td>
<td>2.66</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>54.25 ± 12.83</td>
<td>90.5 ± 10.75</td>
<td>8.22</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

**Figure (2):** Comparison of pulmonary function tests between cases and control group.
Table (6): Comparison of erythropoietin, oxygen saturation and hemoglobin between case and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Case group mean ± SD</th>
<th>Control group mean ± SD</th>
<th>St t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex n&amp;%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (82.5)</td>
<td>5 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (17.5)</td>
<td>5 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td>54.88 ± 7.48</td>
<td>53.0 ± 6.57</td>
<td>0.725</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>HB in gm/dl</strong></td>
<td>11.96 ± 1.69</td>
<td>13.25 ± 0.63</td>
<td>2.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>O2 saturation %</strong></td>
<td>89.63 ± 2.88</td>
<td>97.4 ± 0.52</td>
<td>8.44</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>EPO mu/ml</strong></td>
<td>21.92 ± 6.64</td>
<td>9.42 ± 1.5</td>
<td>5.87</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Figure (3): Comparison of erythropoietin, oxygen saturation and hemoglobin between case and control groups.
Table (7): Comparison of Erythropoietin hormone level in COPD patients according to its grading.

<table>
<thead>
<tr>
<th>Grades</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO AE</td>
<td>13.91±0.65</td>
<td>23.49±2.6</td>
<td>31.53±1.98</td>
<td>16.94±1.23</td>
<td>159.74</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>EPO R</td>
<td>16.04±0.89</td>
<td>25.68±2.57</td>
<td>33.71±2.16</td>
<td>19.39±1.28</td>
<td>145.6</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

AE: acute exacerbation  
R: remission  
EPO: erythropoietin

Figure (4): Comparison of Erythropoietin hormone level in COPD patients according to its grading.
Table (8): Comparison between EPO hormone level and other variables in COPD patients group with anemia and without anemia.

<table>
<thead>
<tr>
<th></th>
<th>Case group with anemia (19) mean ± SD</th>
<th>Case group without anemia (21) mean ± SD</th>
<th>St t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (89.5)</td>
<td>16 (76.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (10.5)</td>
<td>5 (23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I: Mild</td>
<td>0 (0.0)</td>
<td>4 (19.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>7 (36.8)</td>
<td>3 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>8 (42.1)</td>
<td>2 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV: Very Severe</td>
<td>4 (21.1)</td>
<td>12 (57.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>55.95 ± 7.74</td>
<td>53.9 ± 7.29</td>
<td>0.86</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HB in gm/dl</td>
<td>10.56 ± 0.99</td>
<td>13.23 ± 1.08</td>
<td>8.11</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>O2 saturation AE %</td>
<td>89.16 ± 2.22</td>
<td>90.05 ± 3.37</td>
<td>0.975</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>O2 saturation R %</td>
<td>91.89 ± 2.05</td>
<td>93.1 ± 2.3</td>
<td>1.73</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>EPO AE in mu/ml</td>
<td>25.64 ± 6.28</td>
<td>18.55 ± 5.05</td>
<td>3.95</td>
<td>&lt;0.005</td>
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<tr>
<td>EPO R in mu/ml</td>
<td>27.94 ± 6.33</td>
<td>20.84 ± 4.83</td>
<td>4.01</td>
<td>&lt;0.005</td>
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</table>
**Figure (5):** Comparison between EPO hormone level and other variables in COPD patients group with anemia and without anemia.
Table (9): Comparison of variables during exacerbation and after remission in COPD patients.

<table>
<thead>
<tr>
<th>Among cases (40)</th>
<th>During exacerbation mean ± SD</th>
<th>After remission mean ± SD</th>
<th>Paired t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ saturation %</td>
<td>89.63±2.88</td>
<td>92.53±.24</td>
<td>12.38</td>
<td>&lt;0.005</td>
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<tr>
<td>EPO mu/ml</td>
<td>21.92±6.64</td>
<td>24.21±6.58</td>
<td>16.13</td>
<td>&lt;0.005</td>
</tr>
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</table>

Figure (6): Comparison of variables during exacerbation and after remission in COPD patients.
Table (10): Correlation between EPO hormone level and both Hemoglobin and HCT levels in groups of COPD patients.

<table>
<thead>
<tr>
<th>Among cases</th>
<th>EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>HB in gm/dl</td>
<td>-0.492</td>
</tr>
<tr>
<td>Hct %</td>
<td>-0.516</td>
</tr>
</tbody>
</table>
**Figure (7):** Correlation between EPO hormone level and both Hemoglobine and HCT levels in groups of COPD patients.

(a) $y = -1.9322x + 45.036, \quad R^2 = 0.2424$

(b) $y = -0.6503x + 48.03, \quad R^2 = 0.2667$
Results

Table (11): Correlation between EPO hormone level and Oxygen saturation during exacerbation in COPD patients.

<table>
<thead>
<tr>
<th>Among cases</th>
<th>EPO during acute exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>O2 saturation AE %</td>
<td>-0.352</td>
</tr>
</tbody>
</table>

Figure (8): Correlation between EPO hormone level and Oxygen saturation during exacerbation in COPD patients.
Table (12): Correlation between EPO hormone level and Oxygen saturation during remission in COPD patients.

<table>
<thead>
<tr>
<th>Among cases</th>
<th>EPO during remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2 saturation R %</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td>-0.563</td>
</tr>
</tbody>
</table>

Figure (9): Correlation between EPO hormone level and Oxygen saturation during remission in COPD patients.

\[ y = -0.1917x + 97.165 \]

\[ R^2 = 0.3169 \]
DISCUSSION

COPD is a common preventable and treatable disease, is characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients (GOLD, 2016).

Acute exacerbation of chronic obstructive pulmonary disease is defined as acute event characterized by aworsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medications (GOLD, 2016).

Erythropoietin is an endogenous glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa. Also called hematopoietin or hemopoietin. (The American Heritage ® Stedman’s Medical Dictionary, 2004)

Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase (Jelkmann et al., 1992).

Ninety percent of EPO is produced in the peritubular cells of the adult kidney in response to a decrease in tissue oxygenation. (Koury, Bondurant et al., 1988).
The study was aiming at assessment of the erythropoietin changes in different stages of COPD and AECOPD as COPD is traditionally associated with polycythemia also the assumption that anemia frequently occurs in patients with COPD (Attaran et al., 2009).

This study was created on 50 subjects, 40 COPD patients from those attending the Chest Department at Banha University Hospitals in the period between December 2014 and December 2015 plus 10 age matched apparently healthy control subjects. They were divided into 2 groups:
Group1: 40 patients with COPD, EPO hormone will be measured during exacerbation and after remission.
Group2: 10 apparently healthy subjects.

**Inclusion criteria:**
Patients with COPD diagnosed according to GOLD (2016) criteria.

**Exclusion criteria:**
- History of asthma.
- Malignancy.
- Haematologic disorder.
- Systematic or autoimmune disorder.
- Thyroid disease.
- Liver cirrhosis.
- Heart failure (Ejection fraction <55%).
- Gastrointestinal or other hemorrhage.
- Renal failure.
- History of blood transfusion in the last 4 months

In the present study the patients were randomly selected according to inclusion and exclusion criteria, males were (82.5%) and females were
Discussion

(17.5%) and their mean age was (54.5±7.28) years (Table 2) indicates a higher prevalence of disease among males which may be related to the higher rate of smoking and occupational exposure to pollution among men (kurmi et al., 2010).

In this study pre and post bronchodilator spirometry was done among 40 patients known to have COPD and showed partial reversibility in the FEV1% pred. (less than 12%) confirming the diagnosis of COPD cases (Table 4). There were significant differences in spirometric data between patients and controls depicting that FEV1 % predicted were significantly higher (p< 0.05) in healthy control than COPD patients (Table 5 ang fig. 2).

Based on the results of post bronchodilator FEV1% predicted and according to (GOLD ., 2016) guidelines, (4) of patients (10%) were in stage I disease (FEVI ≥ 80 % predicted ) , (10) of patients (25%) in stage II (FEV1:50-79 % predicted ), (10) of patients (25%) in stage III (FEV1:30- 49 % predicted) and (16) of the patients (40%) were in stage IV (FEV1: < 30% % predicted) (Table 4 and Fig. 1).

In the current study, the level of EPO hormone was found to be higher in COPD patients with mean (21.92±6.64 milliunit/milliliter) compared to control group mean (9.42±1.5 mu/ml) and the difference between them was statistically highly significant (p<0.005) (Table 6 and Fig. 3).

In the current study, the concentration of hemoglobin was lower in COPD cases with mean (11.96±1.69 g/dl) compared to control group hemoglobin mean ( 13.25±0.63 g/dl) and the difference between them was statistically significant (p<0.05) (Table 6 and Fig. 3).
Oxygen saturation percent in COPD patients was lower than control group and its mean in COPD patients was (89.63±2.88 %) while for control was (97.4±0.52 %) and the difference between them was statistically highly significant (p<0.005) (Table 6 and Fig. 3).

These results agree with EL-Korashy et al., (2012) who measured the level of hemoglobin, hematocrit, oxygen saturation in blood and erythropoietin hormone in (41) patients with COPD and ten healthy age and sex matched control subjects and the results showed that mean hemoglobin for COPD cases was (13.82 ± 1.95 g/dL) while for the control it was (14 ± 1.27 g/dl) with no statistical significant. Mean value of Hematocrit was (42.1 ± 6.09 %) for COPD and (43.8 ± 3.19 %) for control and again result was not statistically significant. However oxygenation parameters in ABGs showed statistically significant difference between the COPD patients and the control group  SaO2 was (84.9 ± 14.7 %) and (96.80 ± 1.40 %) for COPD cases and control respectively.

The results of this study were in agreement with Attaran et al., (2009) who found that EPO serum level was higher in COPD patients than control groups.

In the current study, COPD patients were divided into 4 stages according to (GOLD., 2016) and erythropoietin was correlated to degree of severity of COPD in (Table 7 and Fig. 4), the results found that EPO hormone level was higher during remission than exacerbation of COPD patients and difference was statistically highly significant (p=0.005). It was found that EPO hormone levels were low in stage I disease (16.04±0.89 mu/ml) , increased in stage II (25.68±2.57 mu/ml) , while
maximally increased in stage III (33.71±2.16 μ/ml) and then decreased in stage IV (19.39±1.28 μ/ml).

On reflecting these changes on the routinely measured parameters of complete blood picture, the percentage of anemia in stage I disease was (0 %) and increased to (36.8 %) in stage II, reaching (42.1 %) in stage III dropping again to (21.1 %) in stage IV (Table 8).

These results are in agreement with El-Korashy et al., (2012) who found that the erythropoietin level was (15.24 ± 2.6 milliunit/milliliter) in stage I disease, (22.61 ± 5.68 μ/ml) in stage II, (33.59 ± 4 μ/ml) in stage III, then (17.9 ± 3.3 μ/ml) in stage IV. Also the total percentage of anemia in COPD patients was (46.3 %), in comparison to (51.3 %) non anemic and (2.4 %) polycythemic. The percentage of anemia was (27.3 %) in stage I disease, followed by (38.0 %) in stage II, raised to (100 %) in stage III then dropped to (58.33 %) in stage IV.

These results could be explained by an increase in the erythropoietin hormone throughout COPD stages in response to increased percentage of anemia throughout the same stage till a certain point then drop in the erythropoietin level occurred with increased severity of COPD. This was also explained by the fact that with worsening of the condition there may be increased blunting of response to erythropoietin. But with increased severity of COPD the burst of systemic inflammation may lead to decreased erythropoietin hormone level.

The results also agree with John et al., (2005) who found that anemia was diagnosed in (13%) of (101) COPD patients. All anemic COPD patients showed elevated erythropoietin hormone levels (41.8 ± 25.4 U/L vs 16.3 ± 2.9 U/L).
COPD itself may cause anemia as a chronic disease, shortened survival of RBCs as a result of raised level of inflammatory mediators as IL1, IL6, CRP and TNF John et al., (2005). This might occur through shortened RBC survival, iron homeostasis dysregulation and impaired bone marrow erythropoietic response Weiss and Goodnough., (2005). Nutritional derangements in COPD patients were proposed as a cause for anemia Aniwidyaningsih et al., (2008). Also, tobacco smoking and its role in oxidative stress has a role in RBCs production Calverley et al., (1982). Lastly, the role of comorbidities frequently encountered in COPD patients as upper GI bleeding and folate deficiency was proposed however they were largely related to smoking also Attaran et al., (2009). This finding is common in COPD and exaggerated during exacerbation.

Contrary to this study results, Attaran et al., (2009), a study was performed in Iran, the authors worked on Eighty patients with the mean age was (66.48 ± 11.55) years and mean forced expiratory volume in first second (FEV1) of (45.14 ± 16.88 %) predicted were enrolled in this study. Hemoglobin and erythropoietin levels were assessed in all patients, The results showed that anemia of chronic disease was present in (13) of 80 patients (16%). The mean serum levels of EPO were (59 ± 203 (SD) µ/l) and (70.3 ± 255 (SD) µ/l) in anemic and non-anemic COPD patients respectively. Increase in EPO hormone level in non anaemic COPD patients than anaemic and this explained by apart from EPO resistance, Other factors may also contribute to the lower hemoglobin level in COPD patients. Defective EPO production and impaired iron utilization due to factors other than inflammation can be responsible in anemia in COPD patients malnutrition, tobacco smoking (because of its associated oxidative stress) and finally oxygen therapy can theoretically blunt hypoxia-driven erythropoiesis in COPD patients.
In the current study we found that there were a statistically highly significant increase (p<0.005) in EPO hormone level and oxygen saturation during remission than exacerbation Table (9) and Fig. (6).

In agree with this study results, Ernest et al., (2010) who found that Log-Epo plasma levels were significantly lower (0.46 ± 0.32 μ/ml) in AECOPD than in stable COPD (1.05 ± 0.23 μ/ml), smokers (0.95 ± 0.11 μ/ml) and never smokers with normal lung function (0.92 ± 0.19 μ/ml) (p < 0.05 each). Log-Epo increased from (0.49 ± 0.42 μ/ml) during AECOPD to (0.97 ± 0.19 μ/ml) during stability (p < 0.05).

This can be explained by that Epo down-regulation during ECOPD can be explained by the burst of inflammation that occurs during these clinical circumstances, as shown here by a significant increase in leukocyte and neutrophil counts, as well as by the raised concentration of hsCRP during ECOPD. Several pieces of evidence support this proposal. First, in vitro experiments have demonstrated that IL-1 and TNF suppress Epo expression and secretion by activating the transcription factors GATA-2 and NF-κb La et al., (2002). Second, clinical investigations indicate that TNF suppresses Epo secretion in patients with advanced solid tumors and chronic infection Braczkowski et al., (2001). Third, Epo plasma levels in anemic patients who suffer concomitantly of other inflammatory process are often lower than expected in relation to their hemoglobin concentration Jelkmann et al., (1998). Fourth and finally, a significant negative association between Epo plasma levels and both hsCRP and neutrophils in the patients studied here .Interestingly, this inflammatory mechanism appears to overcome the regulation of EPO by oxygen, given that the hypoxemia that occurs during exacerbations of COPD would be a strong stimulus for Epo production Stockmann et al., (2006).
Contrary to this study results, John et al., (2005) who found that EPO hormone level in COPD was similar to that seen in control subjects, except in those patients with chronic respiratory failure, severe nocturnal desaturation or anaemia in whom EPO hormone levels were increased.

In the current study, there was a significant negative correlation between EPO hormone level and both Hemoglobin and HCT levels in COPD patients (Table 10 and Fig.7).

These results are in agreement with El-Korashy et al., (2012), John et al., (2005) they found that all anemic COPD patients showed elevated erythropoietin levels. There was a significant inverse correlation between erythropoietin hormone level and hemoglobin concentration.

Also Ernest et al., (2010) found that log EPO plasma level in stable COPD patients with anemia (1.26 ± 0.27 mu/ml) higher than those stable COPD patients without anemia (1.02 ± 0.21mu/ml) which agree with this study results that EPO hormone level has a negative correlation with hemoglobin concentration.

In agreement with this study results, Despoina Markoulaki et al., (2010) performed a study and measured Hemoglobin (Hb), EPO and serum biomarkers of systemic inflammation [CRP, TNF-α, fibrinogen and IL-6] were assessed at three time points (admission, resolution and stable phases) in a selected cohort of (93) COPD patients. Found that Hemoglobin levels were significantly lower on admission compared to resolution and stable phases (median 12.1 g/dl, vs 13.5 vs 13.4), respectively (p=0.005), whereas EPO was significantly higher on admission compared to resolution and stable phases. EPO and Hb were negatively associated during the acute phase, whereas they were
positively associated during discharge and stable phase. In this observational study they have shown that during admission for AECOPD Hb levels are decreased and EPO levels are increased. Also identified a statistically significant negative association between Hb and EPO. The above association is mainly related to increased IL-6 levels, indicating a possible EPO resistance through the mechanism of increased systemic inflammatory process. This can be explained by mediators of the immune and inflammatory responses, such as TNF-α, IL-6, CRP and interferon-γ are potentially involved in the development of anemia in chronic illness *Crosato et al., (2003)*. The increased levels of inflammatory cytokines lead to a shortened RBC survival, with a demand for a slight increase in RBC production. Under such circumstances, the bone marrow cannot adequately respond to the increased demand for RBCs. This is caused by a relative erythropoietin resistance due to an impaired ability of RBC progenitors to respond to EPO *Weiss et al., (2005)*.

In the current study there was a significant negative correlation between EPO hormone and Oxygen saturation during exacerbation and remission. *(Table 11 and 12 and Fig. 8 and 9).*

In agree with the current study, *EL-Korashy et al., (2012)* found that there was a statistically significant correlation for erythropoietin with age, PaO2 and SaO2 in COPD patients, as he measured the level of EPO hormone in (41) patients with COPD and ten healthy age and sex matched control subjects and the results showed a statistically significant negative correlation between EPO hormone level and PaO2 (p=0.05), and negative correlation between EPO hormone level and SaO2 (p=0.05).
This can be explained by diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase. As the PaO2 of the plasma decreases, EPO hormone concentration will increase *Erslev et al., (1980)*.

In agree with this study also, *Kai et al., (1989)* who investigate the early changes in erythropoietin (EPO) formation in humans in response to hypoxia. Six volunteers were exposed to simulated altitudes of 3,000 and 4,000 m in a decompression chamber for 5.5 h. EPO was measured by radioimmunoassay in serum samples withdrawn every 30 min during altitude exposure and also in two subjects after termination of hypoxia (4,000 m). EPO hormone levels during hypoxia were significantly elevated after 114 and 84 min (3,000 and 4,000 m), rising there after continuously for the period investigated. Mean values increased from (16.0 to 22.5 mu/ml) 3,000 m and from (16.7 to 28.0 mu/ml) 4,000 m. This rise in EPO hormone levels corresponds to 1.8 fold (3,000 m) and 3.0 fold (4000 m) increase in the calculated production rate of the hormone. After termination of hypoxia, EPO levels continued to rise for ~1.5 h and after 3 h declined exponentially with an average half-life time of 5.2h.
SUMMARY

COPD is a common preventable and treatable disease, is characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients (GOLD, 2016).

Acute exacerbation of chronic obstructive pulmonary disease is defined as acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medications (GOLD, 2016).

Erythropoietin is an endogenous glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa. Also called hematopoietin or hemopoietin. (The American Heritage® Stedman's Medical Dictionary., 2004)

Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase (Jelkmann et al., 1992).

It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD (Wedzicha et al., 1983). However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis (Attaran et al., 2009).
The aim of this work is to assess the changes in erythropoietin in COPD patients during exacerbation and after remission.

This study was created on 50 subjects, 40 COPD patients from those attending the Chest Department at Banha University Hospitals in the period between December 2014 and December 2015 plus 10 age matched apparently healthy control subjects. After application of inclusion and exclusion criteria, patients demographic data, pulmonary function results and blood level of erythropoietin hormone (measured by ELISA) were recorded.

It was found that:

- As expected pulmonary function parameters (FEV1% predicted) were significantly lower in patients than in control due to air way obstruction in COPD patients.
- Level of erythropoietin hormone were significantly higher in patients than control, also were significantly higher in grade (II, III) than grade (I, IV) COPD patients.
- Erythropoietin hormone level were significantly higher in anemic than non anemic COPD patients.
- Erythropoietin hormone level were significantly higher during remission than during exacerbation of COPD.
- Level of erythropoietin hormone were significantly inversely related to oxygen saturation & both of HB and HCT in COPD patients.
CONCLUSIONS

From this study, it could be concluded that:

- EPO hormone level significantly higher in COPD patients than in control groups.
- EPO hormone level significantly higher in grade (II, III) than grade (I, IV) COPD patients.
- Anemia is more in male than female and in COPD patients group than control group, COPD with anemia higher in stage (II, III) than stage (I, IV).
- EPO hormone level significantly higher in anemic than non-anemic COPD patients.
- EPO hormone level significantly higher during remission than during exacerbation.
- A significant negative correlation between EPO hormone level and Oxygen saturation and both HB & HCT levels in COPD patients.
RECOMMENDATIONS

From this study, it can be recommended that:

- Further studies should be performed on wide scale in stable COPD patients and patients in exacerbation to assess EPO hormone level in such patients.
- Subsequent studies are needed to assess the level of EPO hormone in other inflammatory airway diseases and hypoxemic diseases as bronchial asthma.
- Studies to evaluate the role of EPO hormone as therapeutic target of anemia in COPD.
- Further studies to explain other causes of EPO resistance in COPD patients.
- Further studies to evaluate other hormonal changes in COPD.
- Subsequent studies to evaluate EPO hormone level in COPD patients with polycythemia.
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**Mills, P.R., Davies, R.J. and Devalia, J.L. (1999):** Airway epithelial cells, cytokines and pollutants. Am J Respir Crit Care Med; 160: S38-43.


References


References


References


**References**


References


1) Demographic data & EPO hormone level of COPD patients:

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<th>Age( yr)</th>
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<th>Stage</th>
<th>02% AE</th>
<th>O2% R</th>
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<tbody>
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AE: acute exacerbation  R: remission

2) Demographic data & EPO hormone level of control group:

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المملوء العبري

الملخص العبري

السدي الرنيني المزمن هو من الأمراض المنتشرة التي يمكن الوقاية منها والعلاج الجزئي منه ويميتيز بإعاقة تدفق الهواء التي لا يمكن عكسها تماما. فإنه ينتج عن تفاعل التهابي لدخان السجائر والأمراض الحبيبية. ان تفاقم المرض واصطحابه بأمراض أخرى يؤدي إلى زيادة الخطورة في المرضي.

أما عن حالات تهدى المرض فهي عبارة عن زيادة في سوء الأعراض المصاحبة للمريض عن المعدل اليومي الذي اعتاد عليه المريض والتي تحتاج إلى تغيير وتكييف في علاج المرض.

ان هرمون الارثروبويتين يعد هرمون بروتيني سكري داخلى ويعتبر المؤثر الأول في عملية زيادة عدد كريات الدم الحمراء، وهو يعتبر من الاعشار الخلوية في الخلايا الام لكرات الدم الحمراء في نواة العظم، ووزنه الجزيئي 34 كيلو لتر، وله اسماء اخرى مثل هيموبويتين أو هيماتوبويتين.

ويعيد انخفاض نسبة الأوكسجين في الشرايين المصاحبه لمرض فقر الدم أو نقص الأكسجين هو حافزا رئيسي لانقاذ هرمون الارثروبويتين وعادة ما ينتج زيادة هائلة.

كان من المعترف عليه منذ فترة طويلة أن مرض السدي الرنيني المزمنه يسبب كثرة كريات الدم الحمراء الناجم عن انخفاض الأوكسجين في الحالات المقدمه من مرض الانسداد الرنسي المزمن. ومع ذلك، فقد تبين في العديد من الدراسات أن لدى بعض مرضى السدي الرنينية المزمنة فقر في كريات الدم الحمراء بدلا من كثرة كريات الدم الحمراء.

الهدف من هذه الرسالة هو: دراسة نسبة هرمون الارثروبويتين في الدم في مرضى السدي الرنيني المزمن أثناء التفاهمة وبعد خمود المرض.

وتم إجراء هذه الدراسة بقسم الأمراض الصدرية بمستشفى بنها الجامعى على عدد خمسين شخصا منهم أربعين مريضا يعانون من مرض السدي الرنيني المزمن واثناء أفراد أصحاب في الفترة ما بين ديسمبر 2014 وديسمبر 2015. بعد تطبيق معايير التضمن والاستثناء والمواصفات المطلوبة وعمل وظائف التنفس وقياس نسبة هرمون الارثروبويتين بالدم بواسطة جهاز الاليزة.
الملخص العربي

ويجدر بالذكر...

- نتائج اختبار قياس وظائف التنفس معدلاتها في المرضى بمرض السده الرئوية المزمنه كانت أقل بكثير من الأفراد الأصحاء.
- مستوى هرمون الإريثروبويتين أعلى في المرضى بمرض السده الرئوي المزمن، وكان أيضا أعلى في المراحل (الثانية والثالثة) من حدة المرض عن المراحل (الأولى والرابع).
- كانت نسبة هرمون الإريثروبويتين أعلى في المرضى بالفقر الدم من الذين لا يعانون من فقر الدم.
- كانت نسبة هرمون الإريثروبويتين أعلى خلال شموع حدة المرض أكثر من أثناء تفاهم المرض.
- كانت نسبة هرمون الإريثروبويتين تتناوب تناسبا عكسيا مع نسبة الأكسجين في الدم.

وقد خلصت الرسالة إلى:

- نسبة هرمون الإريثروبويتين أعلى بكثير في مرضى السدة الرئوية المزمنه عن الأفراد الأصحاء.
- نسبة هرمون الإريثروبويتين أعلى في المراحل (الثانية والثالثة) من حدة المرض عن المراحل (الأولى والرابع).
- مرض فقر الدم أكثر في الذكور عن الإناث وفي مرضى السدة الرئوية المزمنه عن المجموعة الضابطة، مرضى السدة الرئوية المزمنه يعانون من فقر الدم بدرجة أعلى في المراحل (الثانية والثالثة) عن المراحل (الأولى والرابع).
- نسبة هرمون الإريثروبويتين أعلى في المرضى بالفقر الدم من الذين لا يعانون من فقر الدم.
- نسبة هرمون الإريثروبويتين أعلى خلال خمول حدة المرض أكثر من أثناء تفاهم المرض.
- نسبة هرمون الإريثروبويتين تتناوب تناسبا عكسيا مع نسبة الأكسجين في الدم.
- مع كلا من نسبة الهيموجلوبين والهيماتوكريت في الدم.
ونوصي بعد هذه الدراسة بالآتي:

• إجراء دراسات لاحقة على نطاق أوسع في مرضى السدة الرئوية المزمنة أثناء استقرار المرض وأثناء تفاقم المرض لتقييم نسبة هرمون الارثروبويتين في الحالتين.
• إجراء دراسات متتالية لتقييم نسبة هرمون الارثروبويتين في الأمراض المصحوبة بالتهاب الشعب الهوائي وانخفاض نسبة الأكسجين في الدم مثل مرض الربو الشعبي.
• إجراء دراسات لتقييم دور هرمون الارثروبويتين واستخدامه في العلاج من مرض فقر الدم في مرضى السدة الرئوية المزمنة.
• إجراء دراسات لاحقة لتوضيح الأسباب الأخرى لمقاومة عمل هرمون الارثروبويتين في مرضى السدة الرئوية المزمنة.
• إجراء دراسات متتالية لتقييم التغيرات الهرمونية الأخرى في مرض السدة الرئوية المزمنة مع كثرة كريات الدم الحمراء.
تقييم هورمون الارثربيوتين في مرضى السدة الرئوية المزمن أثناء تفاقم المرض وبعد الخمود

رسالة

مقدمته للحصول على درجة الماجستير في الأمراض الصدرية والتدرن

مقدمته من الطبية / سلوى حسن محمد السعيد
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2016