A STUDY OF CARDIAC TROPONIN T- IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY OF CARDIAC TROPONIN T- IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** is the bonafide work of **Dr. P. SATHIYA** in partial fulfilment of the university regulations of the Tamil Nadu Dr.M.G.R Medical University, Chennai, for **M.D General Medicine Branch - I** examination to be held in **April 2015**.

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DECLARATION

I, **Dr. P. SATHIYA,** solemnly declare that, this dissertation "**A STUDY OF CARDIAC TROPONIN T- IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr. R. BALAJINATHAN, M.D.,** Professor, Department of General Medicine, Madurai Medical College, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of **Degree of Doctor of Medicine (M.D.), General Medicine Branch-I,** examination to be held in **April 2015.**

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CONTENTS

ABSTRACT

COPD is a leading cause of morbidity and mortality worldwide. Currently ranked as 4th leading cause of death worldwide.

Objective:

This study was aimed to evaluate the incidence of cTnT elevation in COPD exacerbation patients and to see if cardiac troponin T has prognostic significance during an acute exacerbation of COPD.

Design:

Prospective study

Participants:

Sample of 50 adult patients (both male and female) admitted to Government Rajaji Hospital, Madurai with signs and symptoms of acute exacerbation of COPD.

Methods:

Blood samples for cTnT were measured on admission and 24 hrs later using quantitative assay by ELISA method. Levels above 0.017 µg / L were taken as positive. Demographic data, history & symptoms were recorded. Clinical examination & investigations were done on each patient.

Results:

19 patients had elevated cTnT levels. They were divided into two groups, group 1 included patients with cTnT positive, group 2 with cTnT negative. All

patients had increased breathlessness. Majority was males, M: F = 11.5: 1. 58% were current smokers. Mean duration of COPD was high (6.42yrs) in group 1 as well as mean SpO_2 was 75% (low) in group 1. RA, RV dilation & severe pulmonary hypertension were higher in group 1.

cTnT elevation significantly correlated with ICU admission, need for ventilator, ICU & hospital stay duration.

Conclusion:

cTnT is elevated in significant subset of patients with COPD exacerbation. Among them, COPD duration was high, mean SpO_2 was low. It was an independent predictor of need for ICU admission and ventilator support. Significant difference in length of stay in ICU (or) hospital was found among two groups. It can be used as marker to identify patients at higher risk at the time of admission.

KEY WORDS:

COPD (chronic obstructive pulmonary disease)
Cardiac Troponin T (cTnT)
Exacerbation
Corpulmonale
FEV_1 (Forced expiratory volume at one second)

INTRODUCTION

COPD is a leading cause of morbidity and mortality worldwide. Currently ranked as 4th leading cause of death worldwide, it represents an important public health challenge that is both preventable and treatable.

The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.

World Health Organization (WHO) predicts that it will become the third leading cause of mortality by 2020; owing to decrease in cardiac diseases and stroke over the period 1970–2002, but that of COPD doubled over the same period. It is also associated with significant economic burden.

COPD often coexists with other comorbidities which may have a significant impact on its prognosis. Cardiovascular diseases, osteoporosis, lung cancer, diabetes, metabolic syndrome and depression are among a few of them.

Cardio vascular disease is a major comorbidity in COPD patients and probably the most frequent and most important coexisting illness as

these conditions have many risk factors in common like age, male sex, cigarette smoking, although its actual prevalence is unknown.

Many factors lead to an acute exacerbation, of which bacterial or viral infections are most common, however in many patients the underlying cause remains unrecognised, of which acute LV dysfunction may be one. Its vice versa also holds true that an acute exacerbation, whether or not with a history of corpulmonale, has an increased cardiac burden, but prompt identification remains difficult because of non-specific symptoms and signs, and ECHO is not always feasible to recognise it. However identifying these patients may influence treatment and outcome for many of them. Thus biomarkers like cardiac troponins which can be measured by a simple test and are widely available can help us identify these patients.

This study was aimed to see if cardiac troponin T(cTnT) has prognostic significance during an acute exacerbation of COPD.

AIMS AND OBJECTIVES

1. To evaluate the incidence of cTnT elevation in patients admitted with acute exacerbation of COPD.

2. To study the association of elevated cTnT with

(i) Mortality

(ii) Need for and duration of invasive/non-invasive ventilation.

(iii) Length of stay at the hospital.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

This disease is characterized by limitation of airflow that is progressive and not completely reversible. It is associated with increased chronic inflammatory response in the airways and lungs to exogenous irritable particles and gases.

Type of COPD are:

- Emphysema
- Chronic bronchitis.

Emphysema :

Condition defined as destruction and enlargement of distal airways (alveoli of lung).

Chronic bronchitis :

This is clinically definable condition mainly with long standing cough and sputum production (Phlegm).

Chronic cough for three months duration in each of two consecutive years in a patient (among them other causes for long standing cough should be excluded).

Small airway disease:

It is characterized by narrowing of small airways.

Chronic airway obstruction is needed to diagnose a condition COPD.

STRUCTURE AND FUNCTIONS OF AIRWAYS

Conducting airways (starting from nose upto alveolus) communicate external environment with alveolar space. Cross sectional area of airways increases rapidly from glottis (narrowest part) to $> 300cm^2$ in respiratory bronchioles. This leads to high air speed in larger airways (trachea and bronchi). Patency of airways is maintained by cartilage rings and cough reflex. Normal breath sounds are due to airflow turbulency in larynx and central air pathways.

In small airways, structural stiffness of walls is lacking. Here patency is maintained by elastic fibres surrounding alveoli. They give radial traction. Air speed is slow & silent in small airways. Gas transport occurs mainly by diffusion.

Left side, oblique fissure separates upper and lower lobes. Right side, transverse fissure divides upper and middle lobes, oblique fissure separates middle and lower lobes.

Each lobe is comprised of ≥ 2 bronchopulmonary segments. This is nothing but, lung tissue with main branch of each lobar bronchus.

There are 10 broncho pulmonary segments on right side & 9 on left side.

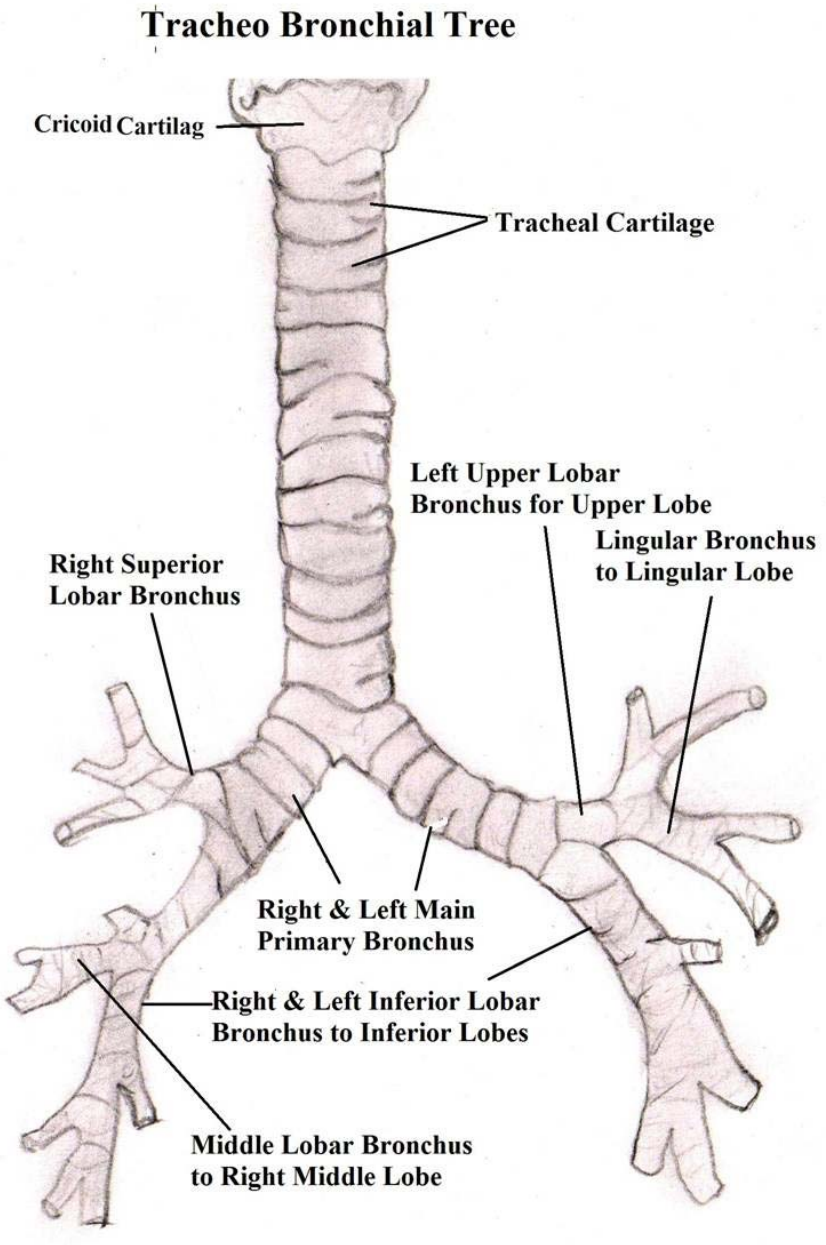


Figure 1: Structure of Tracheobronchial Tree

ACINUS

This is gas exchange unit in lung. It composed of respiratory bronchioles (which are branching) and alveolar spaces. Here, contact between filtered air and pulmonary capillaries occurs. And also oxygen uptake and excretion of CO_2 into lung tissues occur. Lining of alveolar spaces are flattened epithelial cells called Type 1 pneumocytes and few cuboidal cells (Type 2 pneumocytes). Type 2 cells produce surfactant. Its main content is phospholipids, it reduces surface tension and prevent the collapse of alveoli during expiration. Type 2 cells can divide & reconstitute type 1 cells after lung injury.

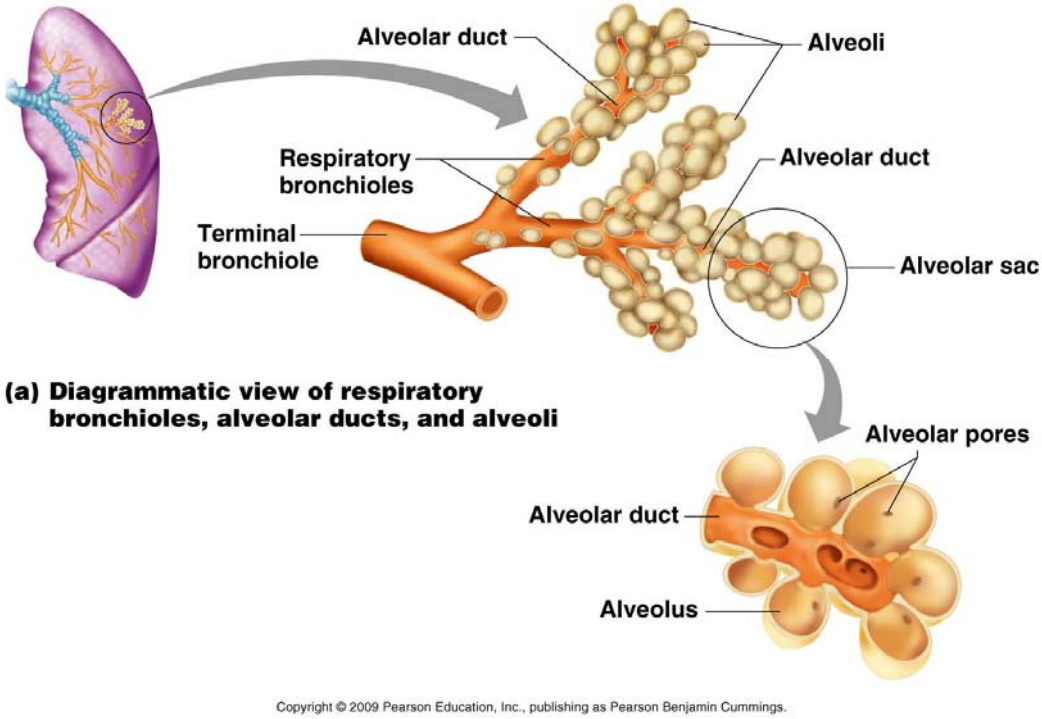


Figure 2 : Structure of Acinus

Distribution of blood circulation and ventilation in lungs is mainly determined by gravity. Major part of perfusion and ventilation going to dependent part only. Hypoxia causes constriction of pulmonary arterioles, CO_2 in airway dilates bronchi. These are useful to maintain ventilation – perfusion match in pulmonary segments.

Diseases that affect ventilation locally causes entry of desaturated, (CO_2 loaded blood) into pulmonary veins. This leads to arterial hypoxemia. Compensatory increased ventilation within remaining normal lungs increases excretion of CO_2 thereby arterial CO_2 come to normal level. But this will not correct hypoxemia (or) increase oxygen uptake. Resultant form of blood gas abnormality is "hypoxia and normocapnia", this is also called 'Type 1 respiratory failure'.

Some causes are

ACUTE

- Asthma (acute)
- Pneumonia
- Pneumothorax
- Pulmonary edema
- Lobar collapse

- Pulmonary embolism
- ARDS.

CHRONIC

- Emphysema
- fibrosis of lung
- Right to Left shunt
- Brain stem lesion.

Severe and diffuse ventilation, perfusion mismatch leads to combination of hypoxia and hypercarbia, otherwise called "Type 2 respiratory failure". Here normal lung is insufficient to correct elevated CO_2. This also results from diseases that reduce total lung ventilation.

The causes include not only lung diseases, also any diseases affecting neuromuscular mechanism of ventilation. (eg) brain injury, polyneuropathies, poisoning with narcotics, myopathies.

Diseases which affect alveolar spaces and capillary membranes {destruction (or) thickening of alveolar capillary membranes} directly impair diffusion of gases. eg. Fibrosis (or) emphysema.

CAUSES OF TYPE 2 RESPIRATORY FAILURE

ACUTE

Acute severe asthma

Upper airway obstruction

Narcotic drugs

Acute COPD exacerbation

Acute neuropathies / paralysis

Fail chest injury

CHRONIC

COPD

Kyphoscoliosis

Sleep apnoea

Myopathies / muscular dystrophies

Ankylosing spondylitis.

Pulmonary circulation is low pressure system. This can accommodate more increase in blood flow that occur during exercise with raising pressure. Pulmonary hypetension occur,

- When pulmonary vessels get obstructed by thrombus
- When destroyed by emphysema
- When destroyed by interstitial inflammation (or) fibrosis

Long standing pulmonary hypertension

⇩

Hypoxia and hypercapnia

⇩

Generalized water and salt retention (corpulmonale)

⇩

Elevated JVP and peripheral oedema.

LUNG DEFENSES

UPPER AIRWAY DEFENSES

In nose, nairs trap large particles in inspired air, small particles are disposed by ciliated columnar epithelium in septum and turbinates towards oropharynx. At the time of cough, forced expiration against closed glottis causes increase in intrathoracic pressure, then it is released suddenly and in explosive manner. Posterior tracheal wall is flexible, it is pushed inwards due to high pressure. This decreases cross sectional areas and increases airspeed to produce effective expectoration. Larynx like sphincter, protect the airway during vomiting and swallowing.

LOWER AIRWAY DEFENSES

Immune system (both innate and adaptive) is important to maintain sterility, structure and functions of lower airways.

Innate immune defense

It is characterized by many nonspecific defense mechanisms. Inhaled particles are trapped by airway mucous and disposed by cilia over mucosal epithelium. Cigarette smoking causes increase in respiratory mucous secretion and it decreases (or) impair mucociliary clearance. This leads to increased risk of lower airway infections like pneumonia.

Defective muociliary function is a key factor in several diseases, which includes Kartagener's syndrome, young's syndrome and primary ciliary dysfunction. These conditions are characterized by recurrent respiratory infections and bronchiectasis.

Airway secretions consist of many substances includes antimicrobial peptides, antioxidants and antiproteinases. These are responsible for opsonisation and bacterial killing, and also important to regulate proteolytic enzymes secreted by inflammatory cells. Neutrophil elastase enzyme is regulated by $\alpha_1$antiproteinase called α_1 antitrypsin. Its deficiency leads to development of premature emphysema.

Cells

Macrophages - these are main phagocytes, engulf organic dusts, microorganisms and other particulate matter. Asbestos (or) silica are inorganic substances which destroy and causes necrosis of macrophages leads to release of proteolytic enzymes, which results in parenchymal damage.

Neutrophis are low in airways, but pulmonary circulation consists marginated pool of neutrophils, so these are easily recruited in response to bacterial infection.

Eosinophils, natural killer cells and mast cells are other cells involved in innate immune response.

Adaptive immune response

This is characterized by specific response and development of memory. Dendritic cells in lungs promote antigen presentation to lymphocytes (T & B cells).

CD_4 T cells stimulate B lymphocytes to produce antibodies (immunoglobulins) that neutralise bacterial toxins and initiate the processes like opsonization and killing of microbes by phagocytosis. Th_2 CD_4 cells promote IgE formation that leads to allergy.

Both of these (innate and adaptive) immune responses are co-ordinated by many cytokines which are important in initiating, terminating and regulation of the responses and coordinating the repair processes.

EPIDEMIOLOGY

COPD is one of the important cause of death worldwide. It occupies fourth leading cause of mortality. It is main cause of morbidity also and results in economic and social burden.

Because of continued exposure to risk factors of COPD and increased life expectancy, prevalence of COPD are expected to increase in coming decades.

65 million people have severe form of COPD (moderate to severe) based on WHO estimate in 2005, more than 3 million persons died of COPD, and it accounts to 5% of all death worldwide. It is known that approximately 90% COPD mortality occurs in developing countries (low to middle income countries).

Mortality due to COPD is expected to increase in next 10 years by more than 30% unless immediate action is taken to control risk factors,

mainly tobacco use. COPD becomes the third leading cause of death from sixth place globally in 2020 according to various estimates.

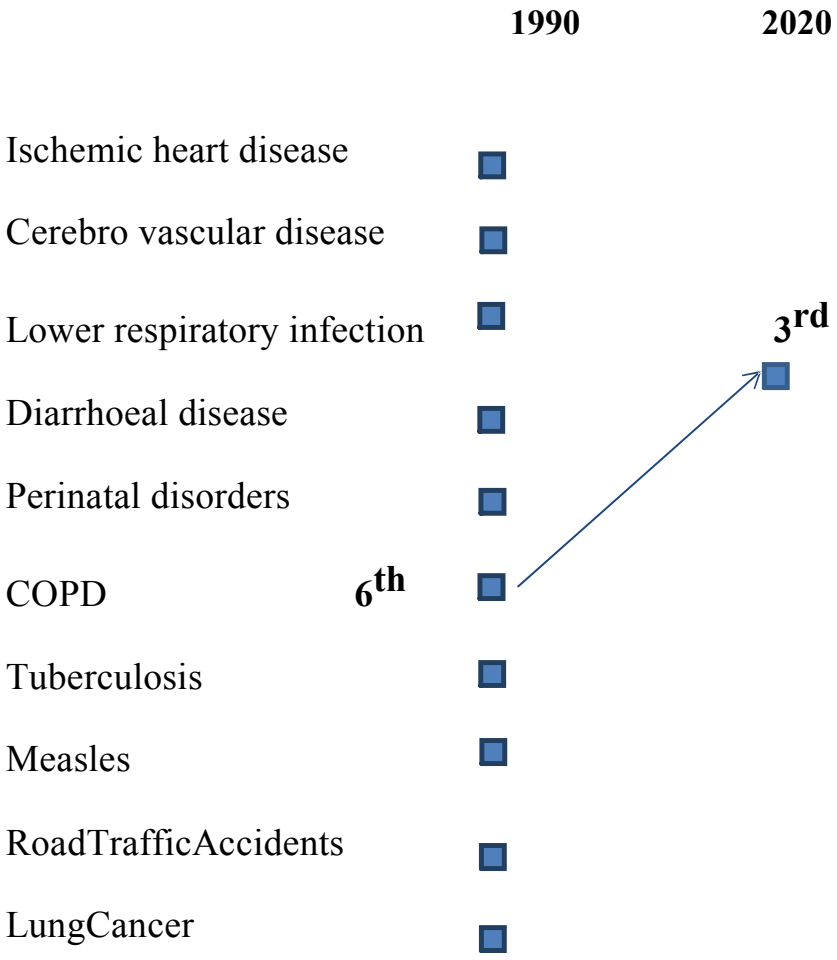


Figure 3: Worldwide mortality 1990-2020

RISK FACTORS OF COPD

Relation between genetic susceptibility and exposure to environmental stimuli play major role in pathogenesis of COPD. Although cigarette smoking is important COPD risk factor, consistent evidence from various epidemiological studies demonstrate that non-smokers may also develop chronic obstruction of airways.

Host factors:

i. Age

ii. Genetic factors

iii. Asthma and airway hyperresponsiveness

Exposures:

- Smoking
- Occupational exposures
- Environmental pollution
- Social – economic status.
- Recurrent respiratory infections (lower airway)
- Childhood illnesses.
- Diet.

1. Cigarette smoking :

This is one of main risk factors of COPD, various longitudinal studies demonstrated that inverse relationship between intensity of cigarette smoking and volume of air exhaled in the first second of forced expiration (FEV1).

Increased intensity of smoking leads to accelerated decline of FEV1. Intensity of smoking expressed in pack years (This is calculated as number of packets of cigarettes smoked per day multiplied by number of smoking years).

This relationship is responsible for increasing prevalence of COPD with increasing age.

Higher smoking rate among males in the reason for higher COPD prevalence among them.

Various environmental and genetic factors contribute to effects of smoking on COPD development. Cigar and pipe smoking are associated with inhalation of low doses of tobacco by products compared to cigarette smoking.

2. Environmental pollution :

Indoor pollution :

For cooking, heating and other household needs, many people worldwide use coal and biomass for energy source. In developing countries, increased prevalence of COPD among non-smoking women is due to biomass fuel for cooking. This is estimated to kill 2 million children and women each year.

Outdoor pollution :

Relationship between outdoor pollution and development of COPD is unclear. But some studies reported that respiratory pathology is more in people living in urban areas when comparing to rural areas. This is mainly due to pollution of air from fossil fuel combustion. Source is motor vehicle emissions in cities.

3. Occupational exposure :

Exposure to dusts and fumes at working place is related to respiratory symptoms and airflow limitation. Specific occupations like coal mining, gold mining, textile dust (eg) cotton are considered as risk factors for COPD. A recent study demonstrated significant relation between coal mine dust exposure and development of emphysema in both smokers and non-smokers.

4. Social economic status :

There is inverse relationship between social economic status and development of COPD. This is related to air pollution, crowding, infections and poor nutrition etc.

5. Respiratory infections :

Respiratory infections are most important causes for COPD exacerbations. But relationship between childhood and adult respiratory infections and development of COPD is unclear.

Host Factors :

1. Genetic factors :

Development of airflow limitation among smokers is largely variable. Alpha 1 antitrypsin deficiency is one of the main genetic risk factor for development of COPD. Other genetic causes also present.

α_1 antitrypsin deficiency :

S allele – involves α_1AT level in slightly reduced range. Z allele – involves severely reduced levels of α_1 AT. M allele – is related with normal levels of α_1 AT. This is common presentation.

Incidence of severe α_1 AT deficiency among COPD patients is 1-2%, these patients mostly develop COPD at early age. Measurement of serum immunologic level of α_1 AT is the commonly used laboratory test to screen α_1AT deficiency.

Pi^z is defined as patients with 2 Z alleles (or) one Z and one null allele. This is the common form of severe α_1 AT deficiency.

Cigarette smoking has major influence on variations of pulmonary functions among Pi^z patients. Combination of severe α_1AT deficiency and cigarette smoking causes development of COPD at early age. Similarly male sex and asthma are important risk factors of COPD among Pi^z individuals.

Treatment for severe α1 AT deficiency is available, with that is infusion therapy of α1AT weekly. Other genes associated with COPD development are minor allele of $MMPI_2$ and portion near the hedge hog interacting protein gene, some genes on chromosome 15.

2. Age and sex :

COPD prevalence raises as age increases, it is common after 40 yrs. More prevalent in men because of changing smoking pattern. Its prevalence increases in women also.

3. Airway hyperresponsiveness :

Various studies compared airway at starting of study and gradual fall in pulmonary function later. This demonstrated that airway

hyperresponsiveness is important factor for further decline in pulmonary function and risk factor for development of COPD.

PATHOPHYSIOLOGY:

Changes occur with COPD development are

- Gradual reduction in forced expiratory flow rate.
- Elevation in residual volume, residual volume and total lung capacity ratio.
- Unequal distribution of ventilation.
- Ventilation – perfusion mismatch.

Airflow limitation (or) obstruction :

This is demonstrated by spirometry with parameters include FEV1 and FVC. COPD patients have decreased ratio of FEV1 / FVC. This decreased FEV1 in COPD rarely show large response to bronchodilator inhalation.

Hyperinflation :

Air trapping is the common finding in COPD patients. This is reflected by increased residual volume and elevated ratio of residual volume to total capacity of lung. These things are routinely measured by pulmonary function testing.

Hyperinflation of chest leads to preservation of maximum expiratory flow of air by decreasing airway resistance.

Adverse effects of hyperinflation :

Flattening of diaphragm leads to decrease in the space of contact between abdominal wall and diaphragm, restriction of rib movements, defective generation of inspiratory pressure.

Gas exchange :

FEV1: reduction of its value to <50% of predicted -> will decrease PaO_2.

Reduction of FEV1 to <25% of predicted, will increase $PaCO_2$.

⇩

This causes development of pulmonary hypertension

⇩

Corpulmonale and right ventricular failure.

PATHOLOGY:

Exposure to cigarette smoke affect all airways of lungs. Large airway changes leads to symptoms like cough and expectoration of sputum. Small airway changes are reason for alteration in physiological parameters. Both these problems occur in patients with COPD.

Large Airway :

Enlargement of mucous glands and hyperplasia of goblet cells resulting from cigarette smoking leads to symptoms [cough and sputum production]. But this does not lead to airway obstruction. Squamous metaplasia may occur in bronchial wall. This is important risk factor for carcinoma development and mucociliary dysfunction. Smooth muscle cells hypertrophy also occur in COPD patients. Airway infections -> lead to influx of neutrophils -> purulent sputum production & generation of neutrophil elastase (one of the important secretogogues).

Small airways :

Small airways with diameter $\leq$ 2mm are major site of airflow resistance. Changes occur in COPD are metaplasia of goblet cells, mononuclear cells infiltration, smooth muscle cells hypertrophy. These

alterations lead to airway lumen narrowing by means of fibrosis, wall edema, increased mucous productions and cellular infiltration.

Decreased surfactant leads to increase in alveolar surface tension and collapse. Destruction of airways (due to proteolytic substances) occur from mononuclear inflammatory cells infiltration.

Lung parenchyma

Emphysema is defined by destruction and dilatation of airways involved in gas exchange (alveoli, ducts, respiratory bronchioles). Changes in airway spaces are perforation and obliteration of air spaces due to coalescences of small air spaces into abnormal and enlarged spaces. Macrophage accumulation in small air spaces is common in smokers.

Emphysema :

Pathologic types are centriacinar and panacinar emphysema.

Centriacinar emphysema is commonly associated with cigarette smoking and it involves enlargement of respiratory bronchioles initially. This type is prominent in upper lobes of lungs and superior segments of lower lobes.

Panacinar emphysema involves abnormal enlargement of air spaces evenly distributed along whole acinar units. This type is commonly associated with α_1 antitrypsin deficiency and involves lower lobes usually.

Pulmonary vasculature :

Chronic hypoxia leads to pulmonary vasoconstriction which produces changes in vessels like intimal hyperplasia and smooth muscle hypertrophy.

PATHOGENESIS

Limitation of airflow way is the most important physiological change in COPD. It happens as a result of both emphysema and small airway obstruction. Development of fibrosis around small airways is important feature in small airways obstruction. Accumulation of collagen occur surrounding airways in the setting of raised collagenase activity.

Pathogenesis of development of emphysema constitutes events that are interrelated with each other.

i. Long standing exposure to cigarette smoke leads to accumulation of inflammatory cells in terminal air spaces.

ii. Release of elastolytic enzymes (Proteinases) causes extra cellular matrix damage in lungs.

iii. Oxidative stress and detachment extracellular matrix from cells lead to structural death of cells.

iv. Air space enlargement occurs due to insufficient repair of extracellular matrix components like elastin.

- Elastase and Antielastase Hypothesis

Elastin is major component forming elastic fibres. This is stable component, most important for maintaining integrity of lung. According to this hypothesis, balance between elastin degrading substances (enzymes) and substances inhibiting their activity (inhibitors) determines pulmonary tissue's susceptibility to destruction, that leads to enlargement of air spaces. Based on this hypothesis, patients with deficient α_1AT (serine proteinase inhibitor) were more likely to develop emphysema than others. As well as introduction of elastase enzyme into an experimental animal leads to development of emphysema.

Other factors identified in the pathogenesis are network of inflammatory and immune cells and other proteinases.

- Inflammation and proteolysis of extra cellular matrix:

Macrophages normally present in lower air spaces. During exposure to oxidative substances from smoke particles, these

macrophages get activated. This leads to production of chemokines and protein lysing substances called proteinases. These recruit other inflammatory cells also.

Oxidant particles from smoke

⇩

Histone deacetylase -2 inactivation

⇩

Acetylated chromatin with nuclear factor κB sites

⇩

Transcription of substances (cytokines and matrix metalloproteinases).

⇩

Accumulation of neutrophils.

CD_8 cells also accumulated in airspaces, this leads to release of protein 10,that in turn causes production of elastase from macrophages. (matrix metalloproteinase 12).

These matrix metalloproteinases along with serine proteinases (important among these is neutrophil elastase) work combindly and causes degradation of other's inhibitors, this finally leads to destruction of lung tissue.

Autoimmune mechanisms are also involved in the pathogenesis of COPD. This was recently identified. In COPD subjects, levels of B lymphocytes and lymphoid follicles are high, especially in patients with advanced disease. Antibodies are identified against elastin.

IgG autoantibodies present in some cases, they bind strongly to respiratory epithelium and responsible for cytotoxicity.

Cigarette smoking leads to disruption of cilia from respiratory epithelial cells and impairment of phagocytosis by macrophages. These changes make the airway susceptible to bacterial infections and recruitment of neutrophils

CELL DEATH

Inflammation and cigarette smoke

⇩

Elevated oxidative stress

⇩

Cell death

⇩

Macrophage uptake of apoptotic cells

⇩

Production of growth factors

⇩

Arrests inflammation

⇩

Repair

Cigarette smoking affects repair process by inhibiting apoptotic cells uptake by macrophages.

INEFFECTIVE REPAIR

Repair of damaged air spaces by adult lung is limited only.

- Process called septation may be reinitiated (this is responsible for formation of alveoli during development).
- Efficacy of stem cells to regenerate lung tissue (this is under investigation only).
- It is difficulty to fully regenerate extra cellular matrix.

CLINICAL SYMPTOMS OF COPD :

- Cough
- Expectoration of sputum
- Breathlessness (mainly exertional)

These are three common symptoms. Dyspnoea may be insidious. Patients may describe breathlessness as increased breathing effort, air hunger, sometimes gasping. These are elicited by proper history taking. Activities with arm work mainly above shoulder level are difficult with COPD patients. In later stages, it is difficult to perform simple works of daily living also.

Worsening of airway obstruction is associated with more frequent COPD exacerbation.

PHYSICAL SIGNS:

In initial stages of disease, physical examination is usually normal. Signs of smoking is evident in most of patients like nicotine stain over teeth, nails and smoke odour on physical examination, most of them show barrel shape chest, increased lung volumes with defective excursion of diaphragm (by percussion). Patients with severe disease may show use of accessory respiratory muscles, usually they prefer peculiar position called tripod position. This is to facilitate accessory respiratory muscle action (intercostals, scalenae and sternomastoid muscles). Patients may present with cyanosis. On auscultation they may have expiratory wheeze. (sign of prolonged expiratory phase).

Emphysema patients are called “Pink puffers”, they are usually non cyanotic (pink) at rest and thin. Accessory muscles active in them. Chronic bronchitis patients are called “Blue bloaters”. They are heavy and blue (Cyanotic).

In later stage of disease:

Patients may show severe wasting, loss of subcutaneous adipose tissue. Reasons for wasting are insufficient oral intake and raised inflammatory mediators like TNFα. This is poor prognostic factor in COPD. Some patients may demonstrate Hoover's sign. This is paradoxical inward movement of chest wall (ribs) during inspiration.

Signs of congestive heart failure may evident in patients with advanced disease. Clubbing is unusual in COPD patients. If it is present, we should exclude lung Ca in them.

Table 1: Spirometric classification of COPD:

Severity	Post bronchodilator FEV1/FVC	FEV1 Predicted (%)
At risk#	>0.7	≥80
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50-80
Severe COPD	≤0.7	30-50
Very severe COPD	≤0.7	≤30

Laboratory investigations :

- Pulmonary function testing has major part in confirming and classifying COPD. Hallmark of airflow obstruction is reduction in

FEV1 and FEV1/FVC ratio. Lung volumes increase with worsening of disease, this leads to increase in lung parameters like residual volume, functional residual capacity and total capacity of lung. In emphysema, destruction of small airways and alveoli leads to reduction in diffusion capacity. Other prognostic factors of COPD are exercise capacity, body mass index and dyspnoea.

- Arterial blood gas analysis may identify hypoxemia. ABG by measuring PCO_2 (arterial) and pH give various information about acid base status and alveolar ventilation. This is also important in evaluation of patients with acute exacerbation.
- Elevated hemotocrit is indicator of chronic hypoxemia and right ventricular enlargement.
- X-ray of COPD patients may helpful in typing COPD.
- Emphysematous changes in X-ray are hyperlucency, reduced parenchymal markings and bullae. Flattened diaphragm and raised lung volume indicate hyperinflation of lungs.

CT scan is useful in establishing diagnosis of emphysema. Testing for α_1AT deficiency in all patients with COPD (or) asthma is important according to recent guidelines. Initial test is it´s measurement in serum. If it is deficient, it will require protease type determination.

ASSESSMENT OF DISEASE:

The goals of assessment of COPD are to know disease severity, its effect on patient's health, to determsine future course of disease like acute exacerbations, hospital admissions and mortality, also to guide treatment modality.

GOLD guidelines use certain factors to determine risk of exacerbations and guide treatment. These include

- Patient's symptoms.
- Past history of exacerbations
- Forced expiratory volume at one second (FEV_1)

Severity of COPD symptoms is assessed by

- CAT – COPD assessment test
- mMRC - modified medical research council.

In previous 1 yr, number of acute exacerbations can be used to determine future events.

- History of 0 (or) 1 exacerbation in past 1 year → low risk group for future exacerbation.
- ≥ 2 exacerbation in past 1 year → grouped as high risk.

Lung dysfunction severity is assessed based on FEV_1 value after broncho dilation using GOLD guidelines. Stages in GOLD classification are at risk to very severe disease.

Group A patients

Low risk group, GOLD stage 1 (or) 2 [mild (or) moderate limitation of air flow] and / or 0 (or) 1 acute exacerbation per 1 yr, mMRC grade 0-1 (or) CAT score <10.

Group B patients

Low risk category, stage 1 (or) 2 in GOLD classification, and / or 0-1 exacerbation of disease per year and mMRC grade ≥2, (or) CAT ≥10.

Group C patients

High risk group, GOLD stage 3 (or) 4 [severe (or) very severe airflow obstruction] and/or ≥2 exacerbations per year and mMRC grade 0-1 or CAT score < 10.

Group D Patients

High risk category, GOLD staging 3 (or) 4 and / or ≥2 acute exacerbation of disease and mMRC grade ≥2 (or) CAT Score ≥10.

TREATMENT

Stable COPD :

i. Abstinence from smoking.

ii. Treatment with oxygen for longstanding hypoxemic patients

iii. For emphysema cases, surgeries involving lung volume reduction. Only, treatment with inhaled corticosteroids may affect the death rate. All other treatment modalities are mainly aimed at improve patient's symptoms and decrease the acute exacerbations frequency.

Smoking cessation :

This is most important and effective intervention to decrease the risk of COPD development as well as to arrest the progression of disease.

Pharmacological interventions available to stop smoking are

- Bupropion (antidepressant drug)
- Replacement treatment with nicotine [Chewing gum, patches (transdermal), nasal spray and inhalers are available forms.]
- Nicotinic acid receptor agonist and antagonist drug ─ varenicline.

Most of the occupationally acquired respiratory problems can be controlled through variety of methods, mainly focused at decreasing the burden of inhalation of particles and gases. Decreasing the risk from environmental air pollution is difficult and it needs combination of public policy and protective measures taken by individual patients.

Bronchodilators :

- Treatment with bronchodilators are key to symptoms management in patients with COPD.
- Inhalation route of therapy – preferred than parentral route as side effects are low.
- Drugs like β2 agonist, theophylline and anticholinergics are used. Combination (or) choice of individual therapy depends on availability of drug and patient's response to drug (like control of symptoms and side effects).

Anticholinergic drugs :

Drugs like ipratropium bromide and Tiotropium are used.

Ipratropium – produces symptom relief and causes acute increase in FEV_1value.

Tiotropium is long acting drug. It gives symptomatic relief and decreases the frequency of exacerbation.

Some studies demonstrated that mortality rate is reduced in tiotropium treated patients compared to ipratropium treated group, but this didn't approach statistical significance. Side effects are lower with inhaled anticholinergic drugs.

Beta 2 Agonists :

These drugs give symptomatic relief. Side effects are increase in heart rate and tremor. Long acting drugs like salmeterol (inhalation form) is much beneficial as ipratropium bromide. More convenient compared to short acting β2 agonist. Combination of β2 agonists and inhaled anticholinergic drugs demonstrated additional benefit than single agent alone.

Treatment with inhalational steroids reduce the frequency of exacerbation by nearly 25%. But its effect on mortality rate is being controversial. Side effects are candidiasis in orophrynx and loss of bone mineral density. They are mainly useful in COPD patients with more frequent disease exacerbation and those who show significant improvement (or) reversibility of symptoms with inhalational bronchodilators.

Oral steroids :

Chronic therapy with oral steroids for COPD patients is not advisable, because risk / benefit ratio is not favourable. Long standing steroid treatment is related with important side effect like osteoporosis, increased infection risk, impaired glucose tolerance and cataract.

Theophylline :

Moderate improvement in vital capacity and air flow rate during expiration occur with theophylline. In severe COPD patients, it produces mild improvement in O_2 and CO_2 levels (arterial). Side effects are nausea, tremor and increase in heart rate. To minimize theophylline toxicity, monitoring it's level in blood is important.

Oxygen

O_2 therapy is the only pharmacological measure demonstrated to decrease the death rates among COPD patients unequivocally. Resting hypoxemia is defined as O_2 saturation $\leq 88\%$ at rest (or) $< 90\%$ with signs of Corpulmonale (or) pulmonary vascular hypertension. Among these patients, use of O_2 therapy has beneficial effect on mortality rate. Benefit depends on (or) propotional to O_2 usage time (hours or days). Oxygen therapy available as portable systems.

Other drugs :

N- acetyl cysteine – it is mucolytic and has antioxidant properties. It's effect on improving lung function and decreasing exacerbation is doubtful.

α_1AT therapy - it is available in intravenous form. Some studies (trial), not clearly demonstrated its effect on reducing decline of lung function. Patient with serum level of α_1AT 11 μm requires α_1 AT therapy. Severe α_1 AT deficiency state with normal lung function does not require α_1 AT therapy.

Non Pharmacological treatment:

Vaccination with influenza vaccine (yearly once) and pneumococcal (Polyvalent) vaccine is important in COPD Patients. This is to reduce infections with these organisms, thereby exacerbations.

Pulmonary Rehabilitation :

This program includes, education of COPD patients and cardiovascular conditioning. It improves patient's life quality, breathlessness, exercise tolerance and decreases hospitalisation.

Lung volume reduction surgery :

This is applied in emphysema patients. Patients with severe pleural disease, pulmonary artery hypertension (>45 mmHg), heart failure, other comorbid problems are excluded. Patients with diffuse emphysematous lesions, FEV1 level <20% of normal value, Diffusion Capacity of Lung for carbon monoxide <20% normal are poor candidates for surgery.

This surgery gives significant benefit in terms of symptoms and mortality in some patients of emphysema. Those with emphysematous changes mainly in upper lobes and reduced exercise tolerance after rehabilitation are commonly benefit from this surgery.

Lung transplantation:

COPD is the second common indication for lung transplantation.

Criteria for selection of candidates are

- Age < 65 yrs.
- Severe disease and suffering even after maximum pharmacological treatment.
- Absence of comorbid problems.

Diffuse emphysematous lesions and pulmonary vascular hypertension are not contraindication for this procedure.

	1 (mild)	2 (moderate)	3 (severe)	4 (very severe)
FEV_1:FVC	<0·70	<0·70	<0·70	<0·70
FEV_1	≥80% of predicted	50–80% of predicted	30–50% of predicted	<30% of predicted or <50% of predicted plus chronic respiratory failure
Treatment	Influenza vaccination and short-acting bronchodilator* when needed	Influenza vaccination, short-acting and ≥1 long-acting bronchodilator* when needed; consider respiratory rehabilitation	Influenza vaccination and short-acting and ≥1 long-acting bronchodilator* when needed, inhaled glucocorticosteroid if repeated exacerbations; consider respiratory rehabilitation	Influenza vaccination and short-acting and ≥1 long-acting bronchodilator* when needed, inhaled glucocorticosteroid if repeated exacerbations, long-term oxygen if chronic respiratory failure occurs; consider respiratory rehabilitation and surgery

GOLD=Global Initiative on Obstructive Lung Disease. *β_2 agonists or anticholinergics.

Table: Therapy at each stage of chronic obstructive pulmonary disease, by GOLD stage[1]

Figure 4: Overview of management of COPD patients according to stage

COPD EXACERBATION:

Acute exacerbations are important feature of natural course of disease process. Average number of acute exacerbations per year is 1.3.

Exacerbations are characterized by episode of symptoms – increased breathlessness, cough and change in sputum amount and character. Other features like fever, sore throat and myalgia may be

present. Airflow limitation and exacerbation episodes are directly related. When airflow obstruction severity increases, exacerbation frequency also will increase.

During each exacerbation episode, we should assess the severity of disease at that time, cause for exacerbation (precipitating factor) and therapeutic options.

COPD exacerbation are costly and morbid event. They severely affect the patient's life quality. It may lead to permanent loss of pulmonary function. Hospital admissions due to disease exacerbations occupy major part of economic cost. Mortality due to acute exacerbation reach upto 10% and 25% of patients may require ICU admissions and ventilator support. Prevention of exacerbation, early identification and effective management are most important to decrease the burden of COPD.

Precipitating factors :

A variety of precipitating factors may cause final process of increased airway inflammation and symptoms. Among these, infection of airway and air pollution are commonly identifiable factors. Bacterial infections are important one, but viral infections are also present in 1/3 of disease exacerbations. No cause is found in 20-35% of cases.

Despite of common contribution from bacterial infections, prophylactic antibiotic treatment has not show significant benefit against exacerbations.

Treatment with inhalational steroids decreased exacerbation frequency by 20-35% in most studies. Oral glucocorticoids (chronic therapy) are not advisable for prophylaxis.

Influenza vaccine has some role in decreasing exacerbations in COPD.

LV dysfunction may also a cause for disease exacerbation, as well as during acute exacerbation of COPD, cardiac burden increases, LV dysfunction also occurs. But its identification is difficult due to non specific signs and symptoms. ECHO evaluation is not possible during exacerbation. Recognizing these patients may affect the treatment and prognosis of them. So biomarkers such as cardiac specific troponins can be useful to recognize these patients. It is measured by simple and easily available laboratory tests.

Assessment of exacerbation :

We should assess the severity of disease exacerbation and also severity of disease (COPD). If any one of components is severe, patient

will need in hospital treatment. History is essential to assess the severity of symptoms like degree of breathlessness, about fever, quality and quantity of sputum and other symptoms like chills, rigor, diarrhea, nausea and vomiting.

On physical examination, attention should be given for certain signs (eg) increase in heart rate and respiratory rate, over action of accessory muscles of respiration, cyanosis, ability to talk complete sentences, patient's neurological status.

Chest examination of patients should focus certain things like focal findings, symmetry of chest, added lung sounds, degree of airflow both sides and paradoxical chest and abdominal movements.

X-ray chest is needed in severe COPD patients with more distress. 25% of those patients have features of pneumonia (or) congestive cardiac failure in X-ray.

Arterial – blood gas analysis is required for late stage COPD, those with hypercarbia history, alteration in mental status and severe exacerbation. Hypercarbia (that is $PaCO_2 > 45mmHg$) has significant effect on treatment.

Indications for hospital admission:

Around 50% of disease exacerbations are mild (even not consulted to physicians). Mortality from acute COPD exacerbations raises with development of respiratory acidosis, in patients with other severe comorbid problems and those requiring ventilatory support.

1. Marked increase in intensity of symptoms
2. Underlying severe COPD
3. Onset of new signs like cyanosis, peripheral edema.
4. Failure of response to initial medical management.
5. Presence of other severe comorbid conditions.
6. Frequent exacerbations.
7. Elderly age.
8. Insufficient home support.
9. Severe hypoxemia, hypercarbia and respiratory acidosis.

Treatment of acute COPD exacerbation

Bronchodilators :

Usually patients are managed with inhalational β2 agonist and anticholinergic drugs either separately (or) in combination form. Administration frequency depends on disease severity. Usually treatment given with nebulised therapy. This form of therapy is easier to give in elderly patients and during severe respiratory difficulty. We can add methylxanthines to this regimen.

Antibiotics :

COPD patients are frequently infected with potential microorganisms peculiar for respiratory system. Identification of specific bacterial species responsible for disease exacerbation is difficult. Common bacteria encountered in COPD patients with exacerbation are pneumococcus, moraxella catarrhalis and Hemophilus influenzae. Other agents like mycoplasma pneumoniae, Chlamydia are present in some cases. Selection of antibiotics based on following two things

i) antibiotic agent susceptible to above mentioned organisms

ii) patient's condition.

Glucocorticoids

Treatment with glucocorticoids during hospital admissions, decreases the hospital stay duration, faster recovery and it decreases the frequency of further exacerbations (or) relapse for 6 months period. There is no significant difference in benefit between 2 weeks steroid therapy and 8 weeks course of treatment with steroid. Dose of oral prednisolone according to GOLD guidelines is 30-40mg per day to 10-14 days. Hyperglycemia is commonly encountered complication of steroid therapy.

Oxygen :

Aim of O_2 supplementation is to maintain arterial O_2 saturation ≥90%. Some studies showed that O_2 therapy does not affect minute ventilation in patients with hypercarbia. In some of them, it may cause increase in PCO_2. This is mainly by changing ventilation and perfusion in lungs.

Mechanical ventilation :

If PaCO2 is more than 45mmHg, we should suggest noninvasive positive pressure ventilation. This is initiating factor for NIPPV. It reduces mortality rate sufficiently, decreases intubation need and treatment complications, it reduces hospital stay duration also. Contraindications for NIPPV are hemodynamic instability, altered mental condition, uncooperative patients, large amount of secretions, difficulty in clearing secretions, facial dysmorphism (or) trauma that lead to difficulty in fitting the mask, obese person and burns. Indications for Endotracheal intubation and mechanical ventilation are:

- Severe breathlessness inspite of initial intensive treatment.
- Severe hypoxemia
- Hypercarbia and respiratory acidosis
- Severely altered mental condition.
- Hemodynamic compromise.
- Respiratory failure and arrest.

Aim is to overcome the above mentioned problems. In ventilators, we should maintain sufficient time of expiration and auto PEEP.

17-30% is the mortality rate among patients with mechanical ventilator support during that hospitalization. For elderly patients (age >65 years) who got the intensive care treatment, death rate doubles in subsequent year to 60%.

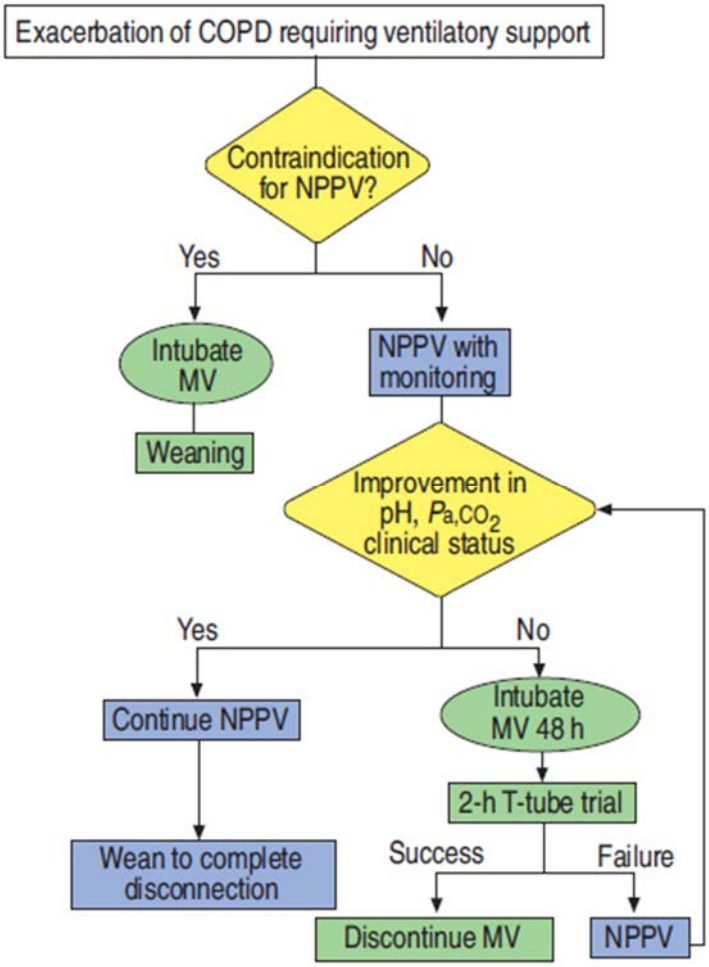


Figure 5: Flow-chart for the use of noninvasive positive pressure ventilation(NIPPV) during exacerbation of chronic obstructive pulmonary disease(COPD) complicated by acute respiratory failure. MV: mechanical ventilation; $PaCO_2$:arterial carbon dioxide tension.

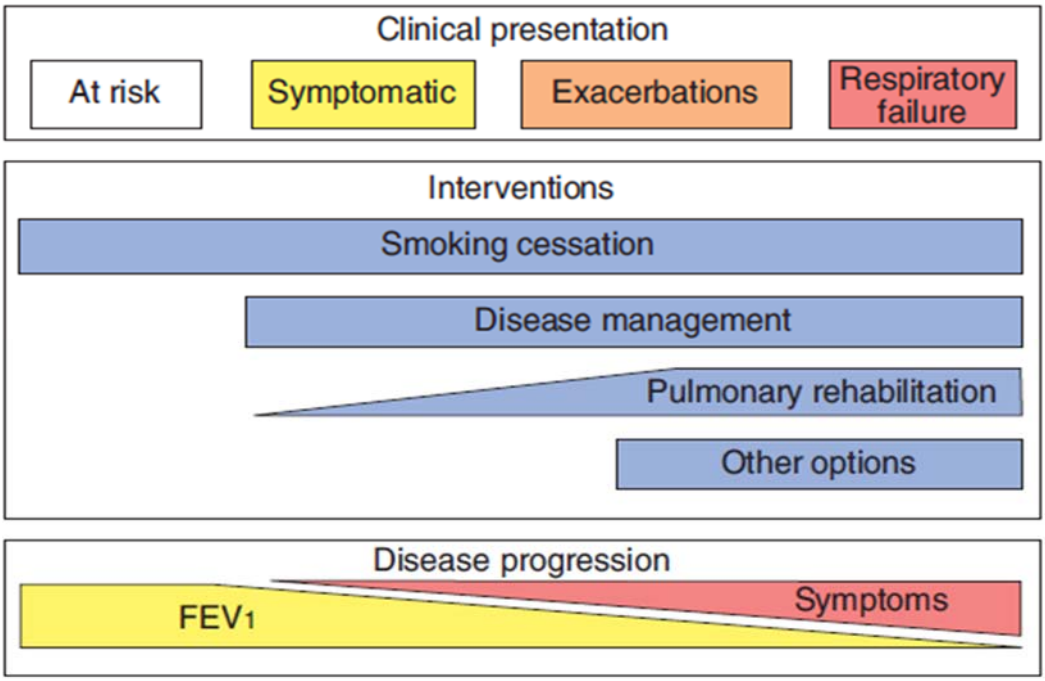


Figure 6: Management of patients in various stages of their disease

Cardiovascular problems in COPD :

Cardio vascular mortality is major cause of mortality in COPD individuals. 12-37% of COPD patients die from cardiovascular disease according to sin et al estimation. Common cardiovascular problems are cardiac failure (Right heart), acute myocardial infarction, arrhythmias, stroke, peripheral vascular disease. Their prevalence is more common in COPD patients compared to non-COPD subjects. Several studies demonstrated the relation between decline of FEV1 and raised risk of cardio vascular disease. Patients with CAD have poor prognosis (survival)

during their admission for acute exacerbation. Elevated cardiac troponins and NT pro-BNP during exacerbation compromise patient's 30 days survival. This message again to show relationship between respiratory and cardiovascular factors during COPD exacerbation.

Pulmonary hypertension and Corpulmonale.

Pulmonary vascular hypertension (PH) with hypoxemic lung problems come under group III of WHO. WHO defines corpulmonale in 1963 as right ventricular hypertrophy resulting from diseases affecting structure and / or functions of lungs except when these pulmonary alterations are due to problems that mainly affect the left side of heart (Eg.) in congenital heart disease.

PH occurs as a result of many factors that includes vasoconstriction of pulmonary vascular system caused by acidemia, alveolar hypoxia, obliteration of pulmonary vasculature from parenchymal pathology and increase in viscosity of blood and raised cardiac output because of polycythemia from hypoxia. Among these, most significant factor is hypoxia. Alterations in airway resistance increase resistance in pulmonary vessels in COPD patients by raising alveolar pressure. Impact of airway resistance over pulmonary arterial pressure is most important when ventilation raises (during COPD exacerbation). In COPD patients,

even slight increase in airflow (eg. during minimal exercise) causes significant increase in pulmonary artery pressure. Alveolar hypoxia is a powerful stimulus for constriction of pulmonary arteries that decreases perfusion (to restore PCO_2). Positive relationship exists between $PaCO_2$ and pulmonary artery pressure in patients with COPD.

Level of pulmonary artery hypertension (even it is mild) is one of the prognostic predictor in COPD patients.

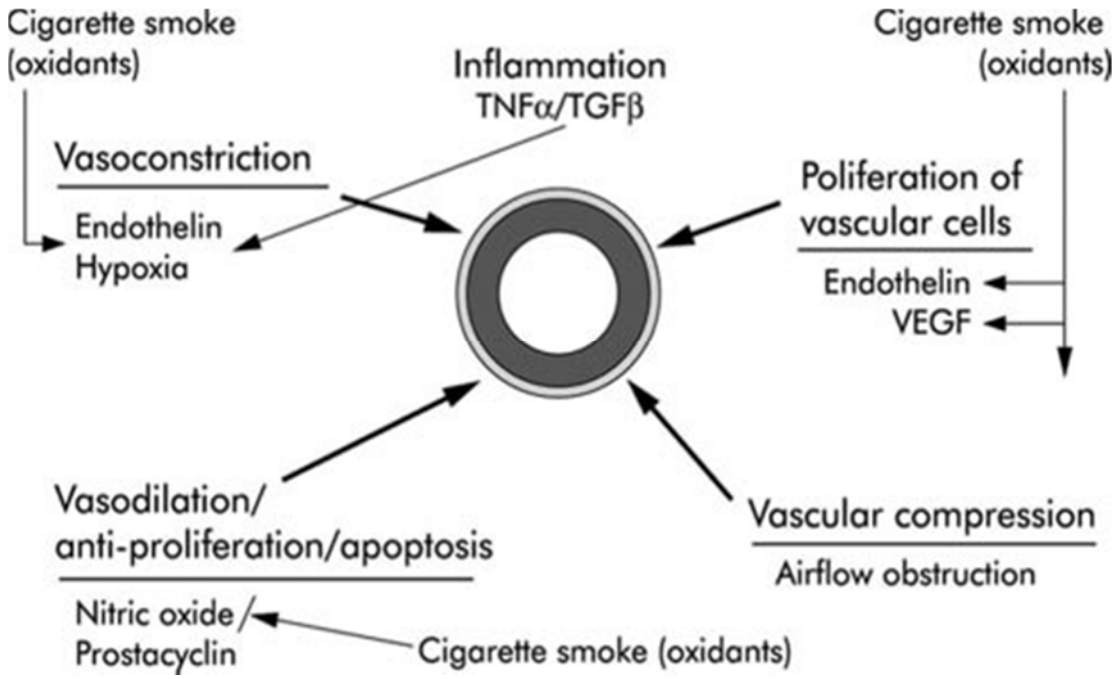


Figure 7: The relation between cigarette smoke and its pulmonary and cardiovascular effects

The above picture shows various processes related with cigarette smoke that causes vasoconstriction, proliferative changes in pulmonary arteriolar walls and vasodilation also. These effects are mainly caused by oxidants (which are present in smoke) that act on walls of blood vessels. It produces vasoconstrictors like endothelins and endothelial growth factor (VEGR). Smoke particles also cause vasodilation by reducing the bioactivity of nitric oxide. Air trapping induced hyperinflation causes compression of vessels and hypoxia induced vasoconstriction occur only when O_2 tension is very low.

Right ventricle :

It is low pressure chamber, it has thin wall and complaint, pumps stroke volume same that of left ventricle. It shares 25% stroke work due to normal low resistance in pulmonary vascular system. RV free wall is supplied by right coronary artery in systole as well as diastole. Long standing pressure overload leads to structural changes in RV (hypertrophy and dilatation), which result in systolic and diastolic dysfunction. Ischemia of right ventricle may occur because of inability to give adequate blood supply to hypertrophied right ventricle by RCA. This is partly due to decreased RCA to RV cavity pressure gradient both during contraction and relaxation phase. This results in corpulmonale later.

Other cardio vascular problems:

Recovery of heart rate after exercise is impaired in patients with spirometric abnormalities. The reason for this is not clear, it may be due to altered autonomic function related with respiratory dysfunction.

Incidence of atrial fibrillation, congestive heart failure, atherosclerosis and myocardial infarction is more among COPD patients compared to non-COPD subjects. This is due to shared genetic and common risk factors like cigarette smoking, poor diet and sedentary life style between COPD and cardio vascular diseases.

Many studies have demonstrated that impaired pulmonary function is accompanied with increased cardiovascular risk (even after adjustment for known risk factors of cardio vascular disease).

Proposed mechanisms are:

1. Systemic inflammation.

Systemic inflammation is increased during COPD exacerbation, due to circulating activated leukocytes and more inflammatory mediators. Causes for systemic inflammation is not clearly defined, but many mechanisms have proposed, these are

- Direct ‘Spill over’ of pulmonary inflammation into systemic circulation.

- Due to the effect of hyper inflated lung

- Tissue hypoxia.

- Muscle dysfunction.

- Stimulation of bone marrow.

Systemic inflammation increases the inflammatory processes in atherosclerosis and thrombosis, there by increases cardio vascular risk. C-reactive protein (CRP) is one of the systemic inflammatory marker. Its level may raise in COPD patients. It is a marker of progression of atherosclerosis and increased mortality in COPD patients. CRP is main risk indicator of cardio vascular disease.

Oxidative stress :

Oxidative stress has major pole in the pathogenesis of atherosclerosis and cardiovascular disease, mainly due to its adverse effect on endothelial cell function (in vessels). But there are no studies available to assess the hypothesis that raised oxidative stress (systemic) leads to more cardiovascular problems in COPD patients.

In COPD, oxidative stress (both pulmonary and systemic) can occur.

Activated neutrophils in peripheral circulation

⇩

Release of ROS (reactive oxygen species)

⇩

Nitrotyrosine and lipid peroxidative products.

(oxidative markers) in plasma.

In COPD exacerbation, oxidative stress increases, along with increased systemic inflammatory response, this causes plaque instability and rupture.

This may disturb fibrinolytic balance leads to thrombosis over ruptured area and acute coronary events.

Activated neutrophils during acute exacerbation release more inflammatory mediators like IL6, TNF α, IL1β. These increase the permeability of cardiac myocytes, leads to apoptosis of cells.

2. Hypoxia :

Heart takes energy from aerobic metabolism. At rest, takes 10-15ml of O_2 per minute per 100g of tissues. This rate is higher than that in brain. For functioning of heart, continuous and adequate amount

of oxygen is necessary and it is so important. O_2 is major determinant of genetic expression over myocardial cells. Oxygen is basic for nitric oxide formation and it affects vascular tone as well as tissue's blood supply.

During acute exacerbation of COPD, broncho constriction, excessive mucous production in airways and wall edema occur. These lead to alveolar hypoxia that in turn causes pulmonary vasoconstriction and hypoxemia.

Hypoxia and tachycardia during exacerbation affects balance between oxygen demand and supply. This leads to myocardial ischemia. (mostly subendocardial).

COPD and chronic respiratory failure are associated with sympathetic nervous system activation. This may be the contributing factor for cardiovascular morbidity and mortality seen in COPD patients. One of the association with COPD is decreased heart rate variability, this is an indicator of abnormal autonomic regulation of cardiac tissue. It predicts the death in older patients.

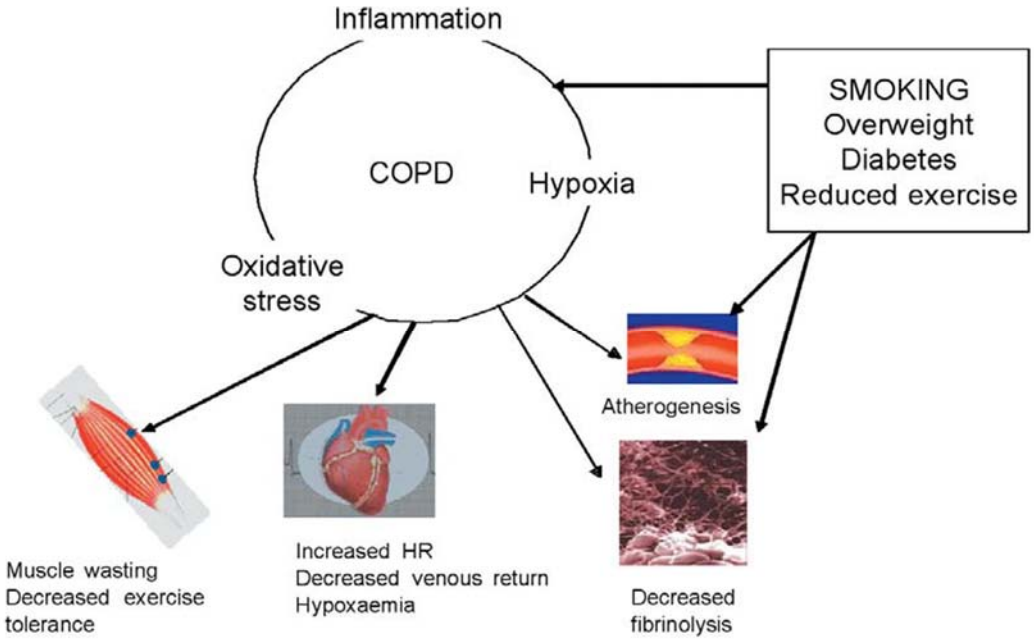


Figure 8: Hypothetical mechanism for a COPD effect on cardio vascular risk

TROPONINS

Troponins are protein molecules, these form integral part of cardiac musculature. They occupy major role in excitation and contraction coupling. They are present in both cardiac and skeletal musculature. They are not present in smooth muscle cells. Composition of these molecules varies between skeletal and cardiac muscles.

3 types of troponins are existing.

i) Troponin I

ii) Troponin T

iii) Troponin C

Troponin I

Binds to actin in thin myofilaments thereby it holds troponin – tropomyosin complex in place.

Troponin T

Binds to tropomyosin, interlock them to produce a troponin – tropomyosin complex.

Troponin C

Binds to calcium ions and produces conformational change in troponin I which results in separation of troponin and tropomyosin complex from actin filaments which exposes binding site for myosin on actin.

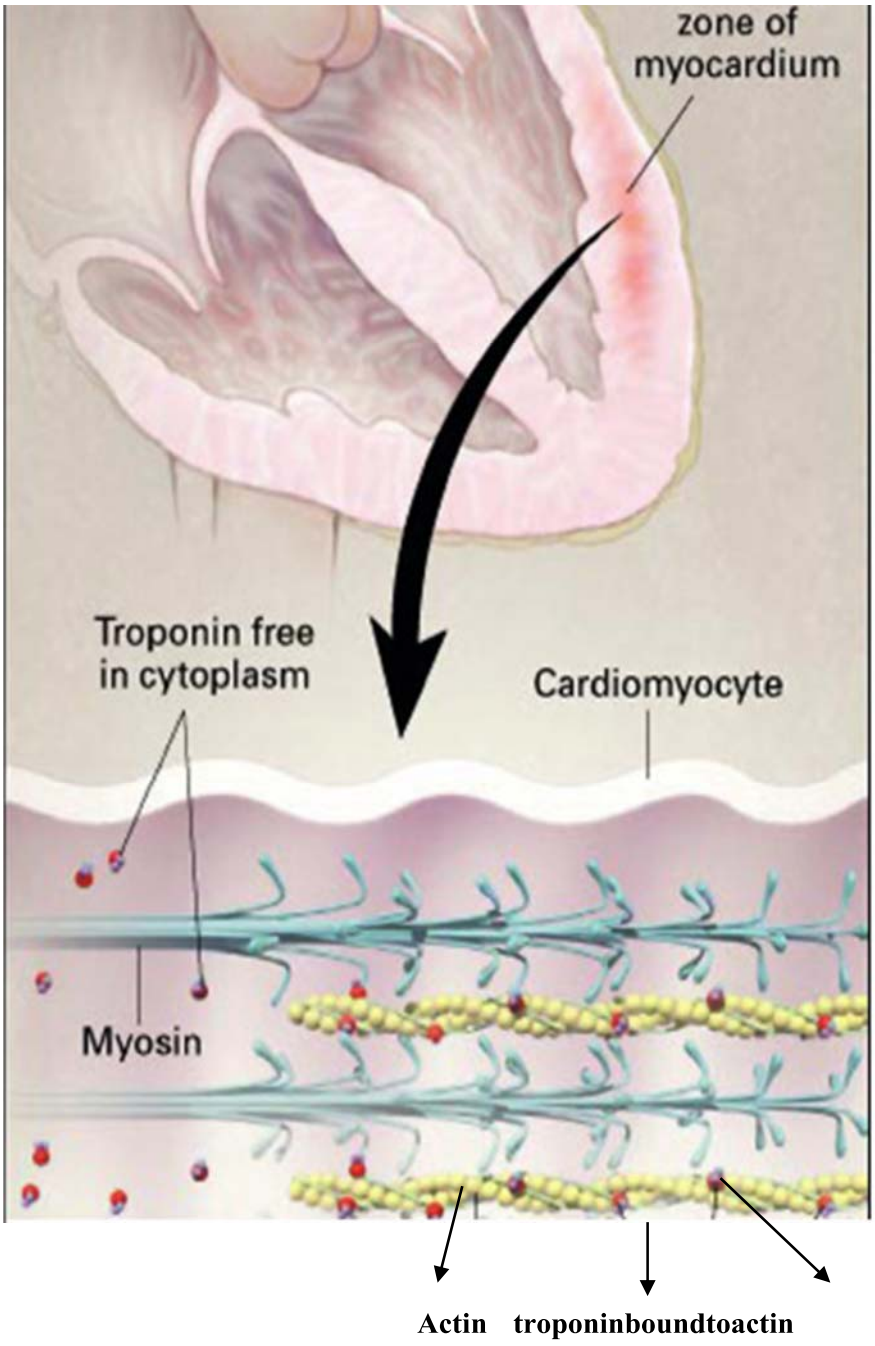


Figure 9: Demonstrating free and bound forms of cardiac troponin

Physiology of cardiac muscle contraction

Action potential

↓

Increase in intracellular calcium ions

↓

Binding of calcium ions to troponin C

↓

Conformational changes in troponin I

↓

Separation of troponin – tropomyosin complex from actin.

↓

Attachment of myosin to binding site on actin

↓

Contraction of cardiac muscle.

Myocardial infarction :

It is the leading cause of death especially in developed countries, its incidence is increased greatly especially in patients with chronic renal failure and COPD.

Definition :

According to 2007 expert consensus document, myocardial infarction is defined as ‘ the detection of rise and/ or fall in cardiac troponins with atleast one value above the 99th percentile of upper reference limit (URL) utilising an assay with less than 10% coefficient variation at the level of detection, together with evidence of ischemia. Infarction was defined as any symptom of ischemia, electrocardiographic

changes suggestive of new ischemia, development of pathological Q wave in electrocardiogram (ECG) or imaging evidence of infarction.

Sudden cardiac death (SCD) with evidence of myocardial ischemia, more than 3 times elevation in cardiac bio-markers in post PTCA patients and more than 5 times cardiac bio-marker elevation in post CABG patients were also included in the definition of myocardial infarction.

Myocardial infarction usually occurs due to the rupture of vulnerable plaque present in epicardial coronary arteries.

Clinical classification of types of myocardial infarction :

There are five types,

- **Type 1** is spontaneous MI due to coronary artery plaque rupture or due to coronary dissection.
- **Type 2** is MI occurring due to increased oxygen demand or decreased supply.
- **Type 3** is sudden cardiac death (SCD) with symptoms of myocardial ischemia, new onset ST elevation, or left bundle branch block (LBBB).
- **Type 4a** is associated with percutaneous coronary intervention (PCI).

- **Type 4b** is associated with stent thrombosis.
- **Type 5** is associated with coronary artery bypass graft (CABG).

Diagnosis of myocardial infarction :

Acute myocardial infarction can diagnosed from clinical signs and symptoms, electrocardiographic changes and estimation of cardiac bio-markers.

Signs and symptoms :

The classical symptom of myocardial infarction is crushing retro-sternal pain which may be described as squeezing or constricting type of pain classically radiating to left arm with impending sense of doom. The pain described here is similar to angina pectoris, but is more severe, lasts more than 20 minutes, and not relieved with rest or nitroglycerine. Pain gradually increased over a period of time and it is not instantaneous pain as with aortic dissection or pulmonary embolism.

The chest discomfort may radiate to the neck, jaw, epigastrium, right arm, shoulders and back. Ischemic pain localised to epigastrium is often misdiagnosed for dyspepsia especially in patients with inferior wall infarction.

Diaphoresis, light headedness, acute confusion, palpitation, dyspnoea, fatigue, indigestion, nausea and vomiting are the associated symptoms given by the patients with acute myocardial infarction. Myocardial infarction can occur without chest pain especially in elderly, patients with diabetes mellitus and in post-operative patients. If the pain is sudden, instantaneous and is radiating to back with unequal pulses on examination , acute aortic dissection should be considered.

In general, general examination findings in patients with myocardial infarction does not add much to the diagnosis. But it is extremely helpful in excluding mimickers of myocardial infarction. They are also useful in risk stratifying the patients and in identifying the impending heart failure. The initial physical findings act as a baseline, such that we can monitor for any complication that develop in the course of disease progression.

Electrocardiography :

ST elevation of 1 mm or more in 2 or more contiguous leads, with reciprocal changes in the contralateral leads is considered to be the definitive electrocardiographic evidence of acute myocardial infarction. In leads V2 and V3, ST elevation of 2 mm in men and 1.5 mm in women are required for diagnosis.

Left bundle branch block (LBBB) in the setting of symptoms that are typically indicative of myocardial infarction is again considered electrocardiographically significant.

Estimation of cardiac bio-markers:

Cardiac bio-markers are considered essential in the diagnosis of myocardial infarction even though they are not considered in the therapeutic flow chart.

The following features are essential for the ideal biochemical marker,

1. Present in high concentration in myocardium
2. Absent in non-cardiac tissue
3. Released rapidly in a linear fashion following myocardial necrosis
4. Present in blood for a relatively longer duration to be easily detectable by inexpensive and universally available assays.

Aspartate aminotransferase, total lactate dehydrogenase, and lactate dehydrogenase isoenzymes were used previously for detecting myocardial necrosis. But their wide tissue distribution limits the specificity for

myocardial necrosis, and therefore these tests are no longer being used in the evaluation of acute MI.

1. Myoglobin :

They are released into the blood stream following myocardial necrosis and are detected in blood between 1 and 4 hours. Hence they are considered to be the earliest markers of myocardial injury. But they are not cardiac specific and hence they are not routinely done for diagnostic workup of myocardial infarction. Their estimation may be helpful in risk stratification of the patient after reperfusion therapy.

2. Creatine kinase (CK) :

Creatine kinase (CK) is carrier protein for high energy phosphates present in muscle fibre. Creatine kinase-MB (CK-MB) is an isoenzyme of creatine kinase which is found abundant in cardiac myocyte. However, even CK-MB constitute 1 – 3 % of the creatine kinase in skeletal muscle. They are also present in small fraction in other organs like uterus, prostate, small bowel and diaphragm. Hence even significant elevation of CK-MB in the presence of injury to one of these organs is considered absurd.

Estimation of creatine kinase is rarely helpful in the diagnosis of acute myocardial infarction in patients with classical chest pain and ECG

changes diagnostic of MI as it takes a minimum of 4 hours to get detected in blood and its initial normal value doesn't exclude MI. They are neither used for therapeutic considerations as well. It takes 4 to 6 hours to get detected in serum and its level peaks at 24 hours, but the peak serum level is believed to occur earlier in patients undergoing successful reperfusion. Both CK and CK-MB get elevated in pericarditis and myocarditis, where there is diffuse ST-T changes as well leading on to diagnostic dilemma. They are helpful in assessing the size of infarct and timing of MI and not for the diagnosis.

False positive raise in creatine kinase is found in skeletal muscle disease and trauma (eg.,rhabdomyolysis).

3. Troponins :

Cardiac troponins are considered to be the gold standard and definitive evidence of myocardial damage and it is the class 1 indication for the diagnosis of myocardial infarction. They are particularly being useful in the diagnosis and management of unstable angina and NSTEMI because of their high sensitivity, easy availability and their ability to be used as bedside test. At present, the lag time between the critical occlusion and detectable elevation in serum limits its usefulness in detecting acute ST-elevation myocardial infarction; however, with the development of

high sensitive troponin T assay which can be detected within one hour of critical coronary occlusion may allow much early detection of myocardial necrosis. Also a single troponin T estimation at 72 hours will indicate the infarct size independent of reperfusion.

Cardiac troponin elevation in the absence of myocardial infarction is found in,

- Congestive cardiac failure
- Myocarditis
- Pulmonary embolism
- Hypertrophic cardiomyopathy
- Aortic dissection
- Cardiac contusion
- Drug toxicity, and
- Acute neurological diseases.

It can also occur due to hemolysis or assay interference with heterophilic antibodies. These heterophilic antibodies can cause false positive test result in 1 in 2000 tests done. To minimize these, non-specific blocking antibodies are being added to modern assays.

Mechanism of Troponin elevation in acute myocardial infarction :

Among the cardiac troponins, troponin-C is expressed in both cardiac and skeletal muscles. In contrast to troponin-C, the amino acid sequences of troponin-I and troponin-T are unique to cardiac muscle and this difference allowed the development of rapid, qualitative assays for detecting troponin-I and troponin-T for detection of myocardial necrosis. Majority of troponins are structurally bound to the contractile apparatus of cardiac myocyte, but approximately 3 – 5 % of troponin-I and 6 – 8 % of troponin-T is free in the cytoplasm.

After the myocyte injury, there is a biphasic raise in the cardiac troponins.

- Phase 1 :

  Corresponds to the release of the cytosolic fraction of troponins.

- Phase 2 :

Corresponds to the gradual dispersion of myofibril bound troponins.

It takes a minimum of 2 – 4 hours for the trans-mural myocardial necrosis to occur, even it takes longer in the presence of collaterals,

preconditioning and intermittent coronary occlusion. Hence they can only be detected 2 – 4 hours after the critical occlusion. It is recommended that blood samples are to be assayed both at presentation and 6 – 9 hours later to optimize both the clinical sensitivity to ruling in MI and specificity to rule out MI. It was previously believed that because of its large molecular weight, troponins are being cleared by reticulo-endothelial system. But recent evidence suggests that troponin-T is fragmented in to smaller molecules which are then excreted via kidneys. This explains why troponin T alone is elevated in case of renal failure.

Troponin sensitivity and specificity:

The sensitivity of troponins increases with time as dictated by troponin kinetics. For troponin-T sensitivity,

At presentation = 25 – 65%,

Between 2 to 6 hours = 59 – 90%,

After 6 – 12 of admission = 100 %.

For troponin-I the sensitivity,

At presentation = less than 45%,

Between 2 to 6 hours = 69 – 82 %,

After 6 – 12 hours = 100 %.

Thus the maximal sensitivity for troponin assay will not reach 100% until 6 hours following myocardial necrosis. This is the reason for assaying troponin between 6 and 12 hours, for establishing the diagnosis of myocardial infarction. Unlike the sensitivity, the specificity of cardiac troponins does not vary significantly over time. The specificity for troponin-I vary between 83 – 98%, while the specificity for troponin-T vary between 86 – 98%.

The negative predictive value for cardiac troponin-I,

At presentation = 85%

After 12 hours = 98%.

The negative predictive value for cardiac troponin-T,

At presentation = 88%

After 12 hours = 99%.

The presence of such high specificity of cardiac troponins, they are associated with very low false positivity rate. This inherent property of cardiac troponins are being used for assessment of myocardial injury in patients with skeletal muscle dystrophy, myositis, crush injuries, marathon

runners, following electrical cardioversion, and in cases of peri-operative myocardial infarction. Other causes for myocardial injury are to be considered when there is an elevated level of cardiac troponins in absence of myocardial infarction.

High sensitivity (hs) troponin assays :

They are helping to overcome the limitations of conventional troponin assays for the earlier diagnosis of myocardial infarction. They got elevated even before 1 hour following myocardial infarction, thus helping to guide in further therapeutic intervention. Advances in immunoassay technology have resulted in multiple second generation troponin-I assays and fourth generation troponin-T assays. In contrast to troponin-T assays which are produced by the single manufacturer, troponin-I assays lack calibrator standardization resulting in significant variation in troponin-I results among different assays.

In one study, at presentation hs-troponin I has

Sensitivity = 90.7%,

Specificity = 90.2%,

Positive predictive value = 87%.

This demonstrates the greater diagnostic accuracy of hs-troponins compared to conventional assays, in particular for the patients who present within 3 hours of symptom onset. The high specificity of hs-troponins along with negative predictive value of 97 – 98 % used to reliably rule out myocardial infarction. This creates an opportunity to rapidly initiate effective medical management, including identifying candidates for early coronary intervention.

Because of the wider availabilities of hs-troponin assays, there is diagnostic shift from unstable angina to NSTEMI.

Prognostic implications of cardiac troponins:

Troponins not only have diagnostic values, they are having prognostic implications as well i.e. patient with clinical evidence of ischemia and raised troponins have a poor prognosis compared to patients without raised troponins. Even patients with stable coronary artery disease, a small rise in hs-troponin indicates the higher incidence of heart failure and cardiovascular death. Recently it has been proved that peak level of troponins indicates the size of the infarct, and is independent predicator of left ventricular function, and adverse cardiac events at one year. There is a statistically significant rise in mortality with the rise in level of troponins. There is relative risk for death of 7.8 among patients

with peak level of troponins, inspite of adjustment for age, baseline variable and ST changes.

COPD and cardiac specific Troponin T:

Risk factors of cardiovascular diseases and cardiac comorbid conditions are frequent in COPD patients. It expresses the severity of disease exacerbation. Harvey et al found that patients with COPD presented with raised troponin levels were elderly people, had decreased oxygen saturation, and more acidotic. Hypercapnoea is more in this group.

Elevated troponin is an independent predictor for requirement of noninvasive mechanical ventilation and death among patients admitted with disease exacerbation.

The amount of energy and requirement of oxygen for respiration are raised during acute COPD exacerbation. The mismatch between oxygen requirement and supply is one of reasons for myocardial injury during exacerbation.

Left ventricular afterload is raised in relation with more negative intrathoracic pressure.

Hypoxia, hypercapnia, progressive worsening of pulmonary hypertension, hyperinflation of lungs, tachycardia, respiratory muscles fatigue -> these are the factors contributing to myocardial damage during COPD exacerbation period.

Increased local as well as systemic inflammation is the main mechanism for myocardial injury and troponin elevation during exacerbation.

MATERIALS AND METHODS

STUDY POPULATION:

This study was conducted in 50 adults (both male and female) admitted to Government Rajaji Hospital, Madurai with signs and symptoms of acute exacerbation of COPD.

INCLUSION CRITERIA:

Patients admitted with acute exacerbation of COPD.

EXCLUSION CRITERIA:

- Pulmonary embolism
- Renal failure
- Myocardial infarction
- Persistent hemodynamic instability requiring inotropic (or) vasoactive support.
- History of cardiac surgery
- History of cardiac resuscitation before admission.

DATA COLLECTION:

Informed written consent obtained.

Basic demographic data, history and symptoms recorded.

Co-morbidities like obesity, hypertension, ischemic heart disease, previous myocardial infarction, atrial fibrillation, and diabetes mellitus were noted. Tobacco users categorized as current, former (>1 year abstinence) or non smokers.

Detailed physical examination including General physical Examination and systemic examination was done on each patient. Glasgow Coma Score was also calculated for each case.

Each patient was subjected to arterial blood gas analysis, chest X-ray, Electrocardiogram (ECG), Echocardiography, spirometry in patients who were able to perform it, and other routine blood/biochemical investigations.

The following were also recorded: Length of hospital stay, including stay in ICU and duration of ventilator support, if any in-hospital mortality rate.

Blood samples for cTnT will be measured on admission and 24 hours later using quantitative assay by ELISA method. Levels above 0.017µg/l were taken as positive.

LABORATORY INVESTIGATIONS :

Each patient was subjected to ABG analysis, chest X-ray, ECG, ECHO, Spirometry and blood for Troponin T, routine and biochemical investigations.

STUDY PROTOCOL

DESIGN OF STUDY : A prospective Study.

PERIOD OF STUDY: August 2014 to October 2014.

COLLABORATING DEPARTMENTS :

Department of Medicine

Department of Thoracic Medicine

Department of Biochemistry.

Department of Cardiology.

ETHICAL CLEARANCE : Obtained.

CONSENT : Individual written and informed consent.

ANALYSIS : Statistical Analysis.

CONFLICT OF INTEREST : Nil

FINANCIAL SUPPORT : Nil

SAMPLE SIZE: 50 patients with acute exacerbation of COPD admitted in Government Rajaji Hospital, Madurai.

RESULTS AND INTERPRETATION

50 patients who met the inclusion and exclusion criteria were included in the study. Among them 46 were males and 4 were females.

Table 2: Gender distribution of patients studied.

Gender	No. of patients	%
Female	4	8.0
Male	46	92.0
Total	50	100.0

Graph 1: showing gender distribution of the study population.

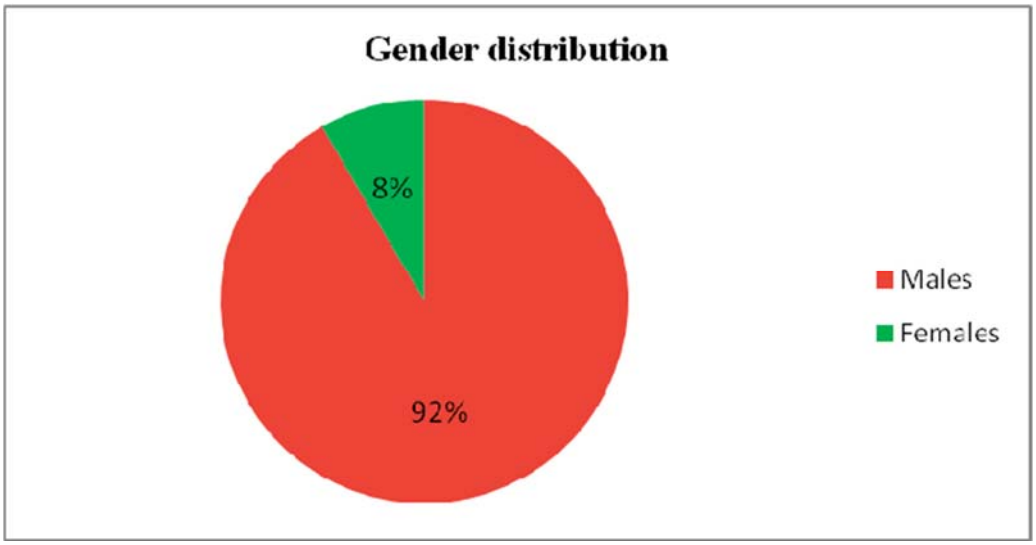
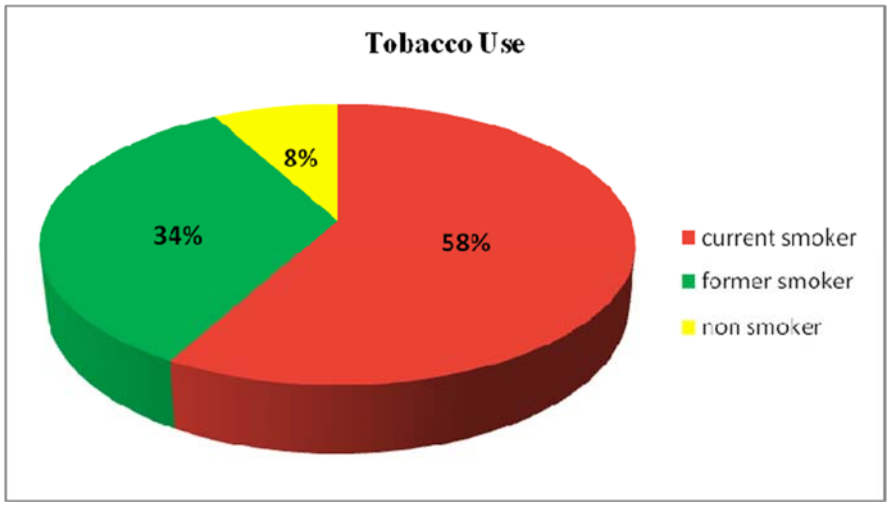


Table 3: Tobacco Use in the patients studied.

Tobacco use	No. of patients	%
Current	29	58.0
Former	17	34.0
Non smoker	4	8.0
Total	50	100.0

Graph 2: Showing division of patients according to their status of Tobacco use.



58% of the patients were current smokers, 34% were former smokers and only 4 % were non-smokers among the patients studied.

Table 4: Showing various presenting complaints in the study population

Symptom	No. of patients	%
Breathlessness	50	100
Cough with increased/ changed sputum	29	58
Fever	13	26
Swelling of lower limbs	7	14
Altered sensorium	2	4

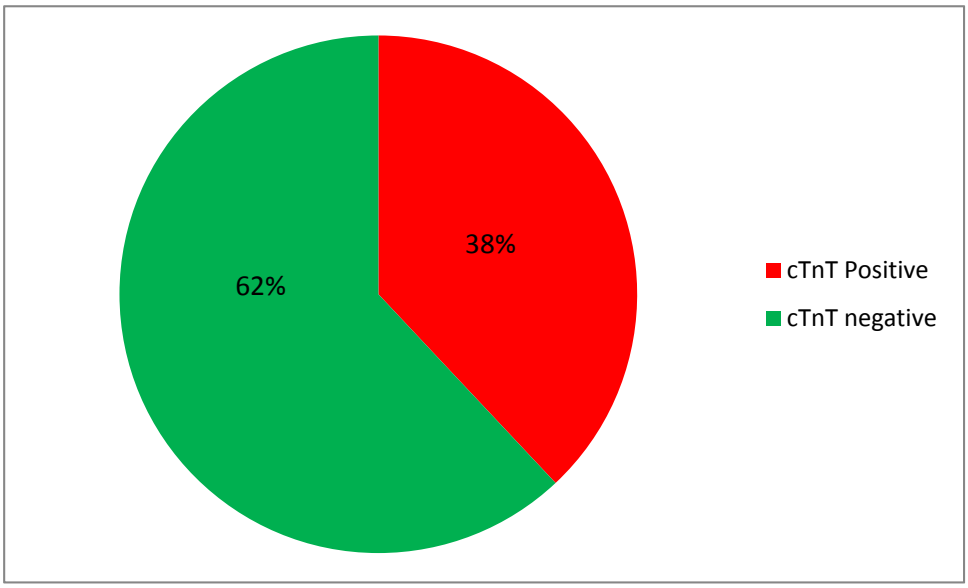
Presenting symptoms:

All patients presented with acute onset of increased breathlessness. 58% had cough with increased amount (or) altered quality of sputum. Fever was one of the presenting complaints in 26% patients. 14% patients had swelling of lower limbs. Altered sensorium due to carbon dioxide narcosis was found in 4%.

Table 5: Patient groups according to their cTnT level.

Troponin	No. of patients	%
Positive (Group 1)	19	38.0
Negative (Group 2)	31	62.0
Total	50	100.0

Graph 3: showing division of patients into 2 groups, cTnT positive and negative.

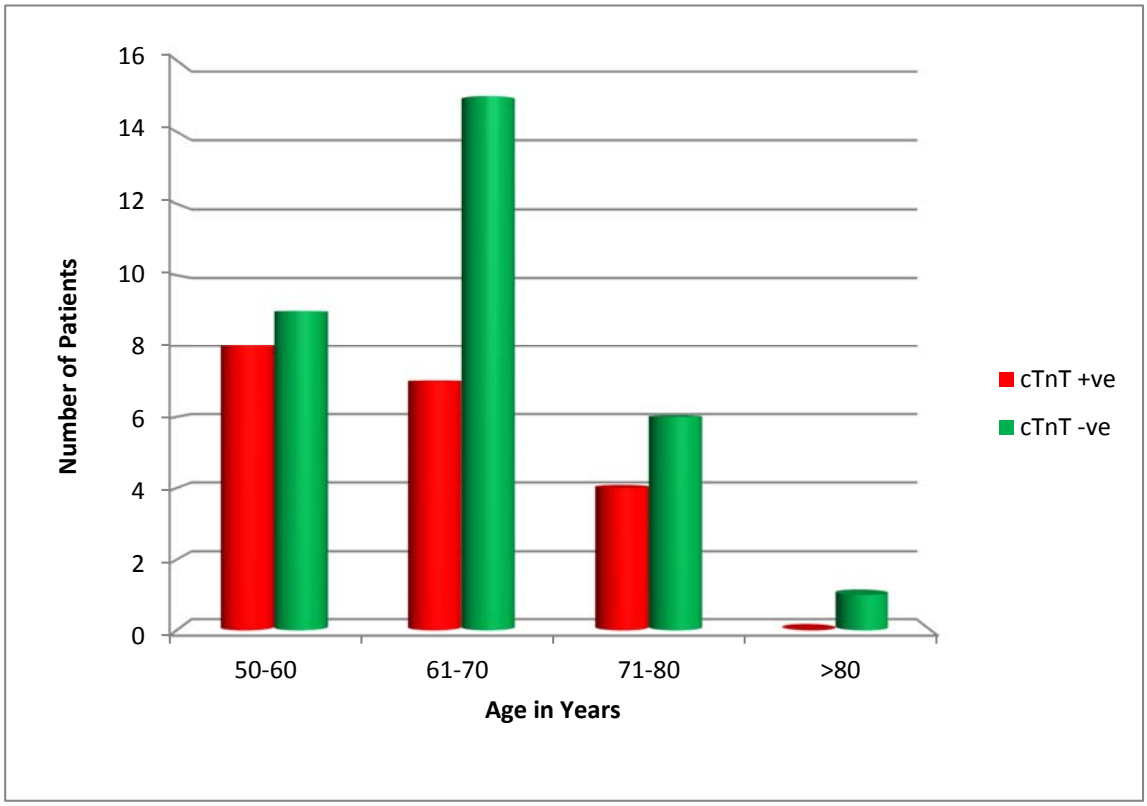


cTnT was found to be positive in 19 patients and negative in 31 patients. Accordingly they were divided into two groups, group1 included patients with cTnT positive and group 2 with cTnT negative.

Table 6: Age distribution of patients according to cTnT levels.

Age in years	cTnT +ve (>0.017 µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	Total (%)
50-60	8(42.1%)	9(29%)	17(34%)
61-70	7(36.8%)	15(48.4%)	22(44%)
71-80	4(21.1%)	6(19.4%)	10(20%)
>80	0(0%)	1(3.2%)	1(2%)
Total	19(100%)	31(100%)	50(100%)

Graph 4 : Showing age distribution of patients according to cTnT levels.



Age:

Patients' age ranged from 55 to 95 yrs. 42% of patients in group 1 were in their 6thdecade, where as in the negative group, 48.5% were in their 7th decade.

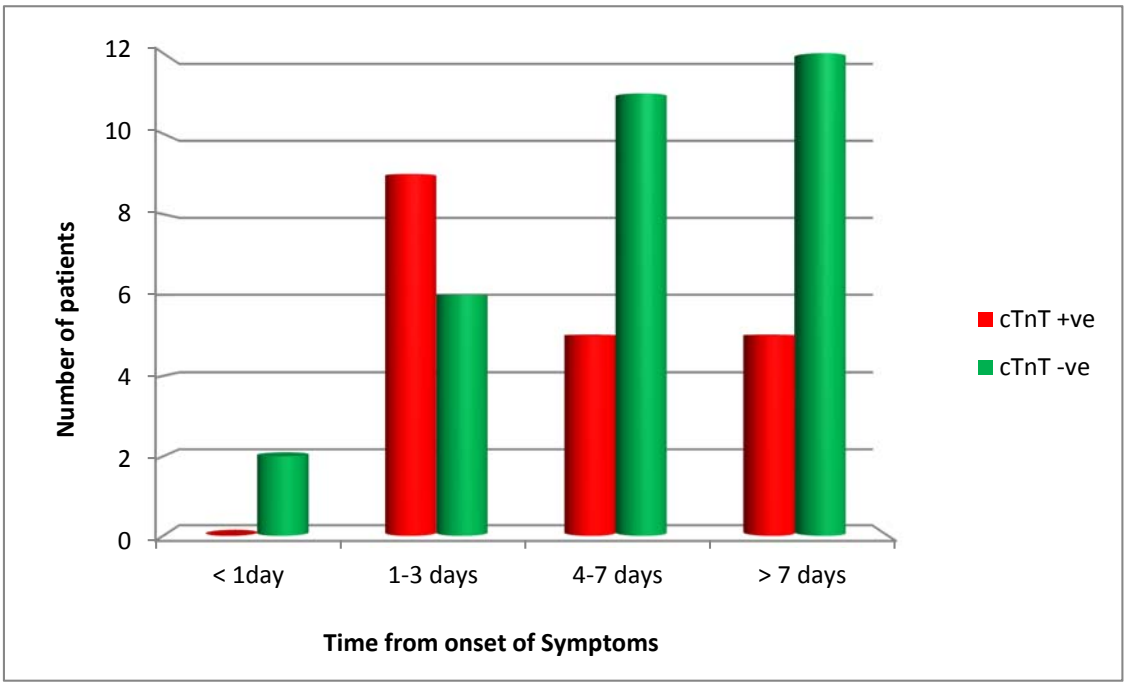
However mean age did not significantly differ among the 2 groups, it was 64.1 yrs in the positive group and 66.72 yrs in the negative group.

Table 7: Time from onset of Symptoms according to cTnT levels.

Time from onset of Symptoms	cTnT +ve (>0.017 µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	Total
< 1day	0	2	2
1-3 days	9	6	15
4-7 days	5	11	16
> 7 days	5	12	17
Total	19	31	50

The time between onset of symptoms to presentation to hospital in majority of patients was 1 to 3 days in group 1, whereas it was > 7 days in group 2 as shown in the graph below.

Graph 5: showing time interval between onset of symptoms to presentation to hospital among the 2 groups.



Mean duration of COPD in group 1 was 6.42 yrs, where as in group 2 it was 3.97 yrs. Co morbidities such as Hypertension, Diabetes are more prevalent in patients in group 1 when compared between both groups.

Patients in both groups were tachypnoiec, had tachycardia and no significant difference was found between them. Mean blood pressure also did not significantly differ among the 2 groups.

However when comparing patients with or without cTropT elevation, difference was found for SpO_2, mean SpO_2 in cTnT positive group was 75% and in cTnT negative group, it was 82.29%, which is significant difference.

There was no significant difference in findings on systemic examination and Glasgow Coma Score among the patients in both groups.

These baseline characteristics of patients in both groups is compared and shown in the table below.

Table 8: Base Line Characteristics of patients on admission according to level of cTnT

Variables	cTnT +ve (>0.017µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	P Value
Trop T (µg/L)	0.272	<0.01	
Age	64.15±7.75	66.72±8.62	0.286
Males	17(89.5%)	29(93.5%)	0.606
Females	2(10.5%)	2(6.5%)	0.606
Current Smokers	9(47.4%)	20(64.5%)	0.232
Disease Duration (Years)	6.42±3.34	3.97±1.94	0.002**
Co Morbidity	10(52.6%)	8(25.8%)	0.055+

HTN	6(31.6%)	5(16.1%)	0.201
DM	5(26.3%)	5(16.1%)	0.382
Clinical Features			
RR	31.79±4.61	30.32±4.90	0.299
HR	108.32±12.42	103.94±11.76	0.217
SBP	123.47±22.91	128.13±16.99	0.415
SpO2	75.00±11.44	82.29±4.86	0.003**
Rhonchi	17(89.5%)	30(96.8%)	0.291
Crackles	13(68.4%)	18(58.1%)	0.464
Silent Chest	6(31.6%)	4(12.9%)	0.109
GCS			
<6.0	1(5.3%)	0	0.388
6-9	2(10.5%)	1(3.2%)	0.549
>9	16(84.2%)	30(96.7%)	0.147

Table 9: Cardiovascular characteristics of patients according to level of cTnT

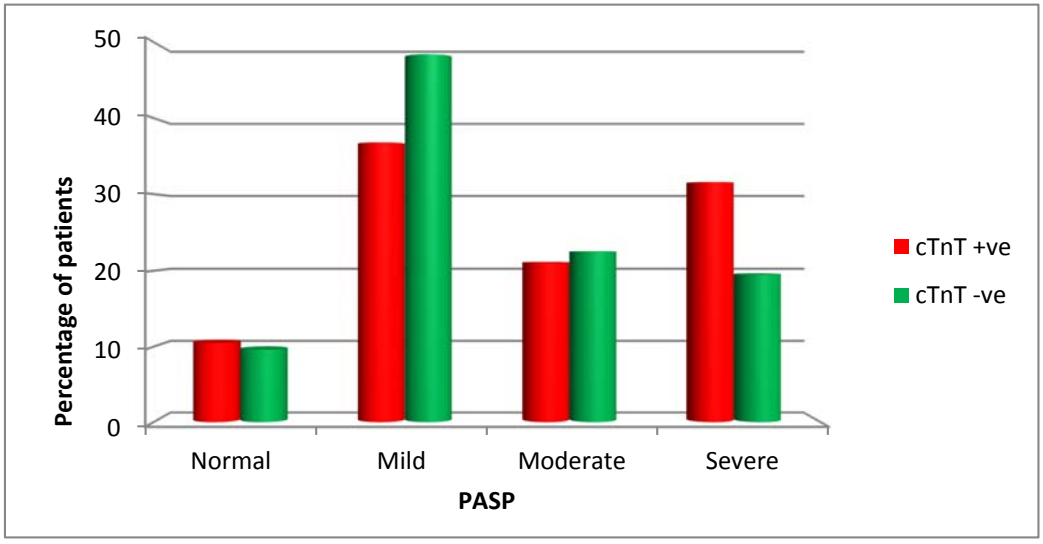
Variables	**cTnT +ve (>0.017 µg/dl) n=19**	**cTnT –ve (<0.017µg/dl) n=31**	**P Value**
ECG			
Sinus tachycardia	14(73.7%)	24(77.42%)	0.764
P Pulmonale	6(31.5%)	14(45.16%)	0.341

Sinus tachycardia was the most common finding on ECG in both the groups, followed by P pulmonale which was seen on ECG in 31.5% of patients with elevated cTnT and 45.2% with cTnT negative.

Table 10: comparing ECHO characteristics of patients in both groups.

Variables	cTnT +ve (>0.017µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	P Value
PASP mmHg			
Normal < 30	2(10.5%)	3(9.6%)	0.914
Mild 31-45	7(36.8%)	15(48.4%)	0.218
Moderate 45-59	4(21.05%)	7(22.5%)	0.859
Severe >60	6(31.59%)	6(19.5%)	0.326
Dilated RA/RV	12 (63.15%)	10(32.25%)	0.033*

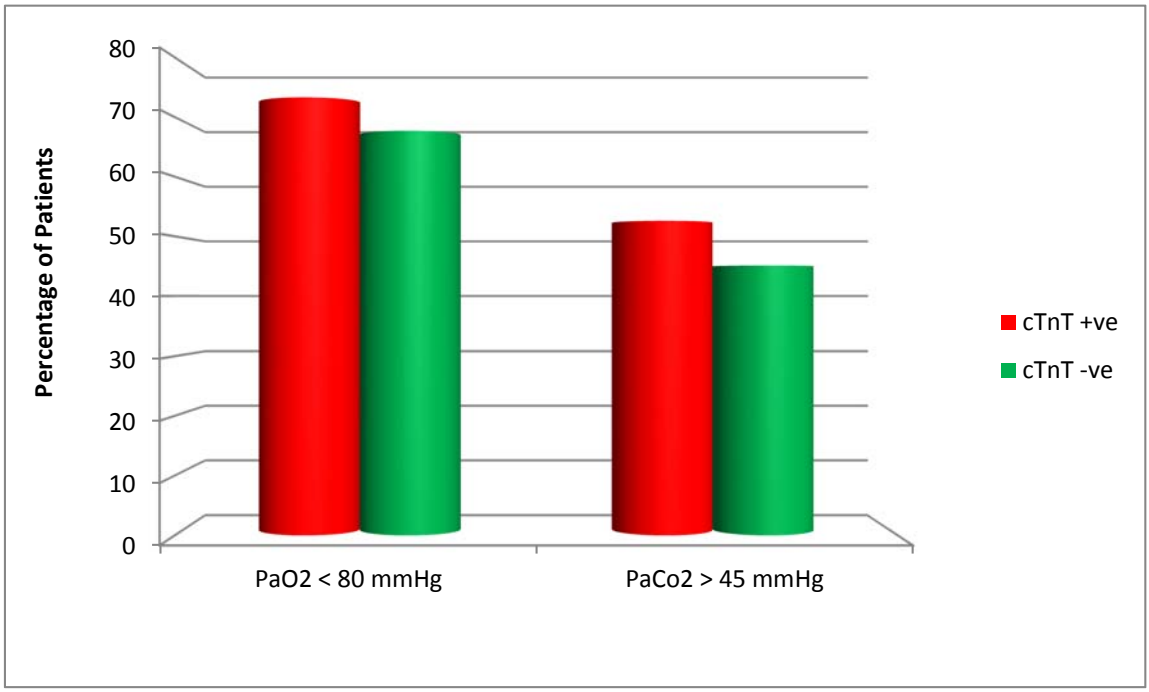
Graph 6: showing distribution of patients according to their PASP level.



On 2D echocardiography, the pulmonary artery systolic pressure (PASP) at rest was high in about 90% patients in both groups. However severe pulmonary hypertension was found in 31.5% of patients with cTnT elevated as compared to 19.5% of patients without elevated cTnT.

Dilated right heart chambers were found in 63.15% patients in group 1 Vs 32.25% patients in group 2.

Graph-7 showing percentage of patients with abnormal blood gases



Blood Gases:

PaO_2 was low (i.e<80 mmHg) in 73.7 % patients in group 1 and 67.7% in group 2. $PaCO_2$ was found to be high (i.e> 45mmHg) in 52.6% in group 1 and 45.1% in group 2.

Table 11: Comparing blood gases according to level of cTnT

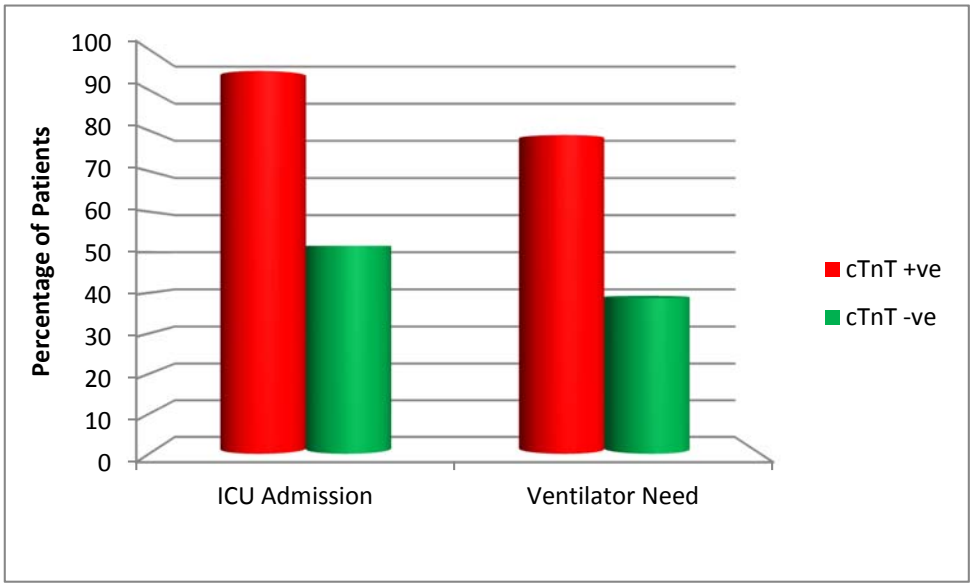
Variables	cTnT +ve (>0.017 µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	P Value
PaO2 mmHg	78.07±46.05	76.77±32.69	0.907
PaCo2 mmHg	54.76±24.19	47.77±23.29	0.315

The mean value for these variables also did not differ significantly among the two groups.

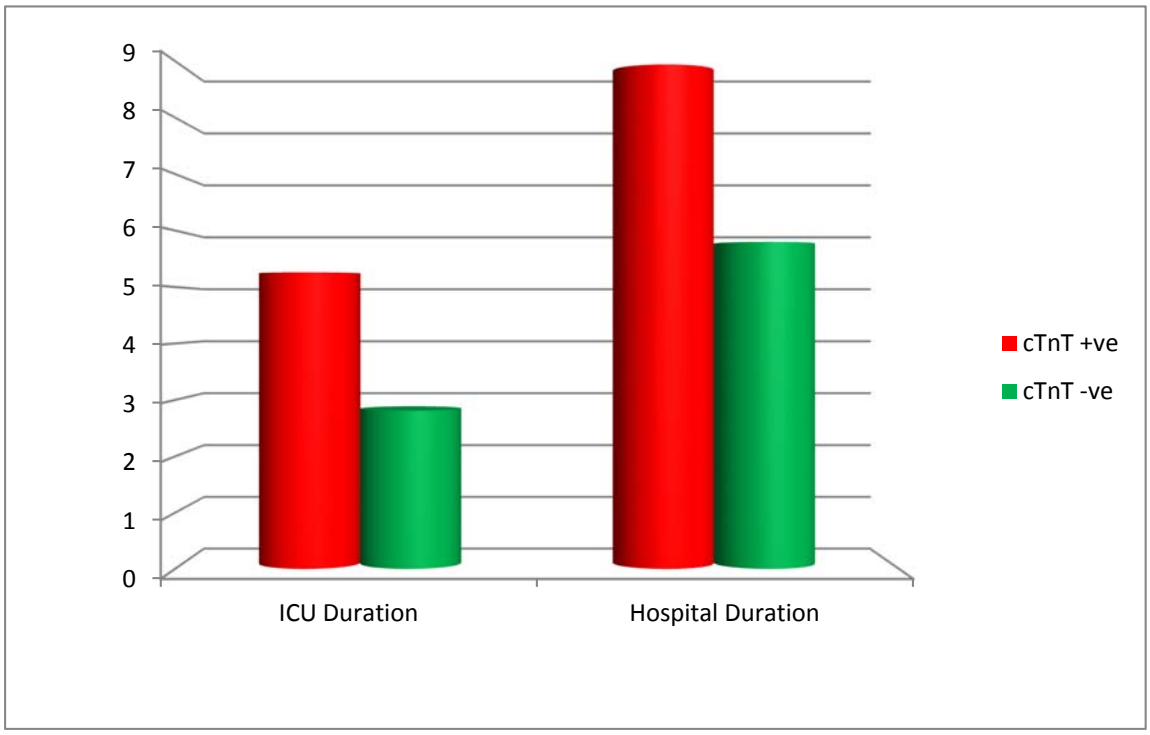
Table 12: Admission to ICU, Need for ventilation, Length of Stay and Mortality of patients according to level of cTnT

Variables	cTnT +ve (>0.017 µg/dl) n=19	cTnT –ve (<0.017µg/dl) n=31	P Value
Admitted to ICU	18(94.7%)	16(51.6%)	0.002**
NIV/ invasive	15(78.9%)	12(38.7%)	0.006**
Duration of ventilator support (median)	4.0	4.0	1.000
Length of stay in days			
In ICU	5.26±2.28	2.81±4.72	0.019
In hospital	8.94±4.46	5.80±3.911	0.012
Mortality	3(15.8%)	2(6.5%)	0.285

Graph 8: comparing the need for ICU admission, ventilator support among both the groups.



Graph 9: Showing mean duration ICU & hospital stay in days



94.7% needed admission to ICU in the group with elevated cTnT, whereas only 51.6% required ICU admission in those without cTnT elevation.

78.9% and 38.7% patients required ventilator support, including both noninvasive and invasive ventilation, among the two groups respectively. However no significant difference was found in the duration of ventilator support required.

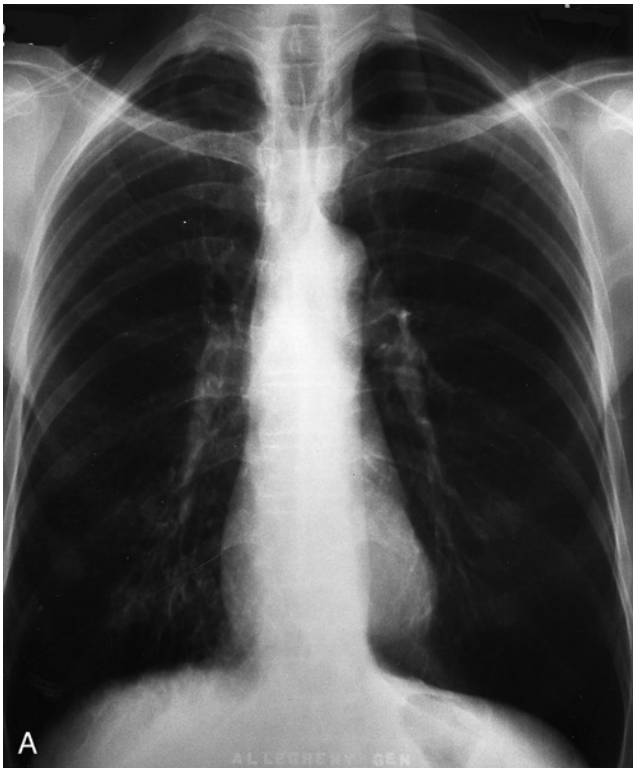
Significant difference was found in the length of ICU stay and hospital stay between two groups.

Mortality:

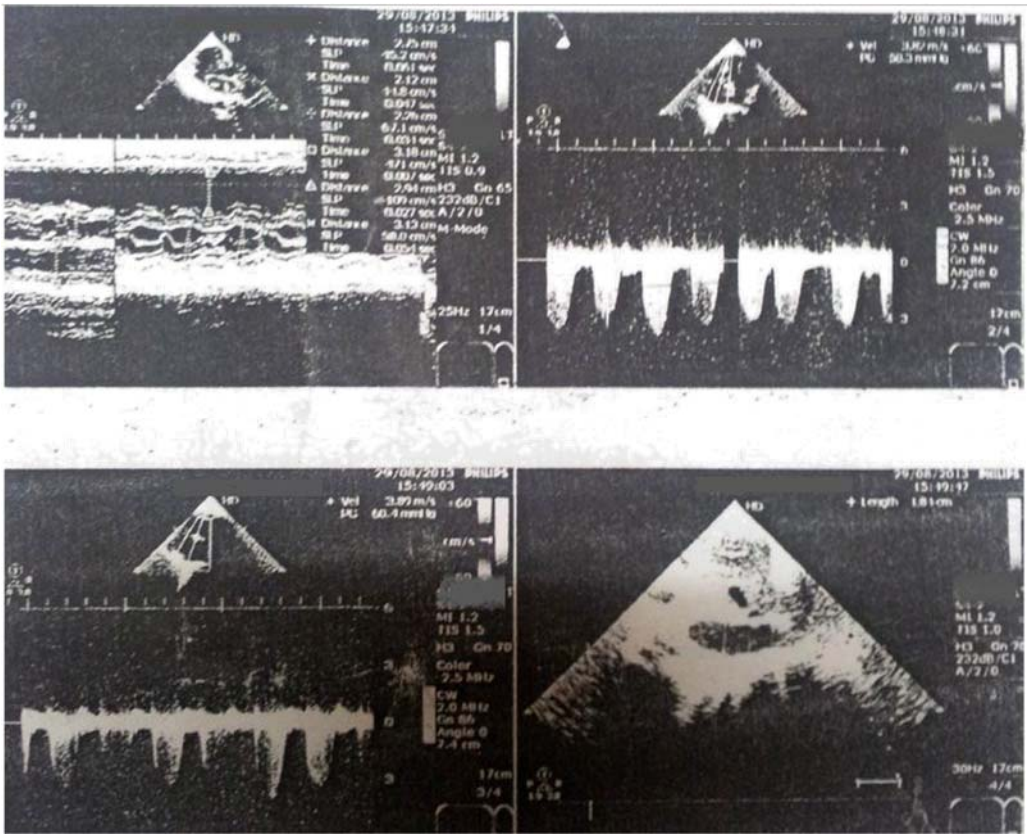
Total of 5 patients died in the study population, three in the 1st group and two in the 2nd group.

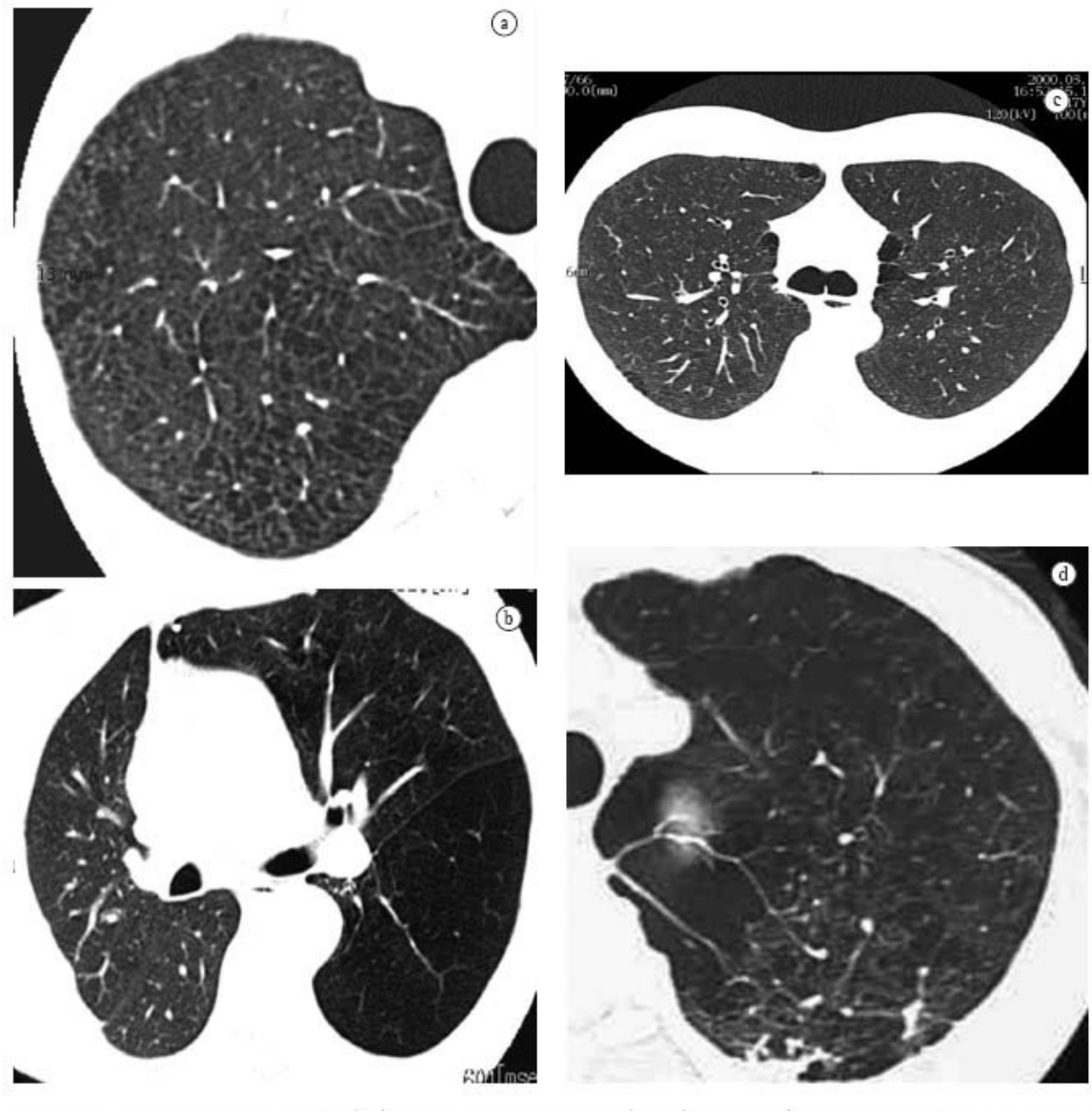
No significant difference was found in the in-hospital mortality rate between the two groups.

Chest X ray PA view of a patient, hyperaerated lung fields suggestive of COPD



ECHO of a patient showing dilated right heart chambers with Pulmonary Hypertension, moderate TR and reduced RV function.





CT and HRCT images: a) representation of centrilobular emphysema. b) representation of panlobular emphysema. c) HRCT scan of a patient with emphysema, with predominant paraseptal lesions. d) HRCT of a patient with irregular emphysema, with some areas of 'scar related'emphysema.

Statistical Methods:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

DISCUSSION

Among the 50 patients included in this study, cTnT was found to be elevated in 19 patients, which corresponds 38%.

This suggests that cardiac injury exists in patients with exacerbation of COPD.

This finding that elevated cardiac troponins occurs in patients with acute exacerbation of COPD is consistent with many studies described, although incidence of cTnT elevation has been different as shown in the table below.

Table 13: comparing the incidence of elevated troponin in patients with acute exacerbation in various studies with present study.

Author and year of publication	Incidence of cardiac troponin elevation
Baillard et al,2003[53]	18%
Martins et al,2009[54]	70%
Hoiseth et al,2011[56]	74%
Brekke et al,2009[57]	27%
Chang et al,2011[58]	16.6%
Present study	38%

There was a significant co-relation with the duration of the disease; patients with elevated cTnT had longer duration.

Elevated cTnT was also associated with higher prevalence of severe pulmonary hypertension and corpulmonale.

Previous studies have reported higher incidence of ventilator support, poor prognosis and increased mortality in patients with elevated cardiac troponin during acute exacerbation of COPD. A study by Baillard et al also showed elevation of cardiac troponins in patients with acute severe exacerbation of COPD was an independent predictor of mortality. Similarly Hoiseth et al showed that elevated hs-cTnT was associated with higher mortality.

Martin et al showed that patients with elevated cardiac troponins had longer hospital stay with greater need for non-invasive ventilation and lower 18 month survival.

In agreement to other studies, in this study there was a strong co-relation with elevated cTnT and need for admission to ICU and ventilator support, as well as ICU stay or hospital stay duration were statistically significant when compared between the two groups.

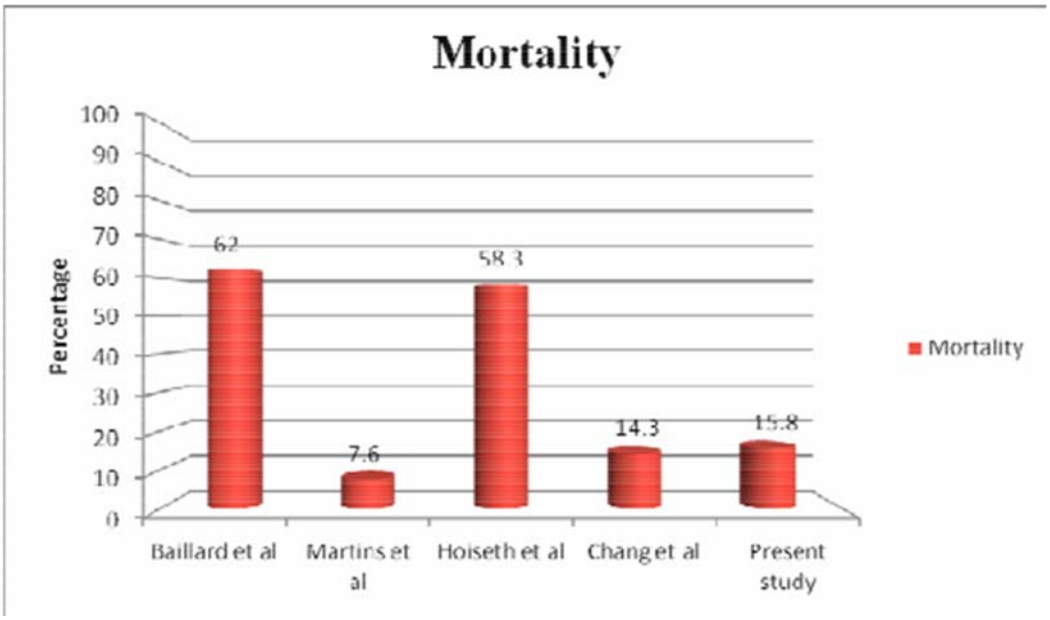
It was also not a strong predictor of in hospital mortality as shown by few studies.

Mortality was longer in patients with elevated cardiac troponins when compared to those without troponin elevation among the studies mentioned below, even if it was not statistically significant.

Table 14: Showing percentage for ventilator support, hospital stay and mortality in patients with elevated cardiac troponins in various studies.

Study	Need for Ventilator	Hospital stay	Mortality
Baillard et al	46%	-	62%
Martins et al	45%	10days	7.6%
Hoiseth et al	-	-	58.3% per 100 patient yrs
Chang et al	-	-	14.3%
Present study	78.9%	8.94days	15.8%

Graph 10: comparing mortality rate in patients with elevated cardiac troponin in different studies.



The above findings suggest that cardiac injury exists in patients with exacerbation of COPD. However the exact mechanism for elevation of cTnT in acute exacerbation of COPD was not within the scope of this study, but it being an enzyme specific for cardiac muscle injury the reasons for its elevation that could be proposed are:

i. Worsening of pulmonary hypertension, RV pressure overload
ii. Hypoxemia, and hypercapnia
iii. Oxidative stress
iv. Increased work of breathing

v. Inflammation(both local and systemic)

vi. Increased left ventricular afterload due to more negative intrathoracic pressure

From prognostic point of view this is an important observation, as we can identify a subgroup of patients at particular risk. When proper cause for elevation is identified, we may actually be picking a subset of patients earlier and if treated appropriately it will influence the long term outcome.

LIMITATIONS:

Due to severe dyspnoea and hypoxia in some of the patients, ABG at the time of admission could not be drawn at room air in them.

This study did not include follow up, hence the long term outcome associated with cTnT elevation could not be evaluated.

CONCLUSION:

- cTnT is elevated in a significant subset of patients with acute exacerbation of COPD.
- These patients had significantly longer duration of COPD, higher incidence of lower SpO_2.
- It was an independent predictor of need for ICU admission and ventilator support.
- Significant difference in length of stay in ICU or hospital was found between both groups.
- It did not predict in-hospital mortality.
- Thus it can be used as a marker to identify patients at higher risk at the time of admission.
- Further studies involving larger number of patients are recommended to evaluate whether long term outcome varies in patients with elevated cTnT.

SUMMARY

50 Patients with acute exacerbation of COPD were studied from August 2014 to October 2014. A male preponderance was found with M:F ratio being 11.5:1. 58% were current smokers and 34% were former smokers.

All patients (100%) presented with increase breathlessness of varying duration. 58% of patients had cough with increased or change in the character of sputum.

19(38%) of the 50 patients were found to have elevated cTnT and were included in group 1, the rest form group 2. Mean age of patients in group1 was 64.1 years and it was 66.72 years in group 2. Mean age in each group did not differ significantly between two groups.

Mean duration of COPD was 6.42 years in group 1 vs 3.97 years in group 2, which is significant difference.

Their mean SPO_2 was also lower compared to patients without elevation of cTnT. Mean SpO_2 was 75% in cTnT elevated group and it was 82.29% in group 2.

Comorbid conditions like diabetes and hypertension were more prevalent in group 1 than in group 2, but they were not correlated significantly.

Comparing the ECHO features of the two groups 31.59% of the patients had severe pulmonary hypertension in group 1, whereas only 19.5% in group 2. RA and RV dilatation was significantly higher in group 1.

PaO_2 was low and $PaCO_2$ was high in larger percentage of patients in group 1 compared to those in group 2. But mean value of these variables did not differ significantly between two groups.

cTnT elevation significantly correlated with ICU admission, need for ventilation, duration of stay in ICU and hospital stay duration. 94.7% of patients required ICU admission in group 1 whereas 51.6% needed admission to ICU in group 2. 78.9% and 38.7% of patients needed mechanical ventilation among two groups respectively.

Although mortality was higher in group 1, it was not statistically significant. Thus cTnT can be taken as a marker to identify high risk patients during acute exacerbation of COPD.

BIBLIOGRAPHY:

1. GOLD: Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease. Updated 2013. www.goldcopd.org (accessed on 15th July 2013)

2. WHO. World health statistics 2008. http://www.who.int/whosis/ whostat/EN_WHS08_Full.pdf (accessed july 20, 2013)

3. Badham C, Practical observations on the Pneumonic Diseases of the poor, Edinburgh medical and surgical journal. 1: 166, 1805.

4. Thomas L Petty. The history of COPD. Int J Chron Obstruct Pulmon Dis.2006:1(1)

5. Lawrence EC, Brigham KL. Chronic cor pulmonale In: Hurst's The Heart. 11th edition. Vol. 2. New York, McGraw-Hill. 2004: 1617-1632.

6. http://en.wikipedia.org/wiki/Chronic_obstructive_pulmonary_disease#History (accessed on 21st july 2013)

7. Paul D White. The Acute Cor Pulmonale. Ann Intern Med. 1935;9(2):115-122.

8. Perry SV. Background to the discovery of troponin and Setsuro Ebashi's contribution to our knowledge of the mechanism of relaxation in striated muscle. Biochem Biophys Res Commun. 2008 Apr 25;369(1):43-8

9. http://www.uptodate.com/contents/chronic-obstructive-pulmonary-disease-definition-clinical-manifestations-diagnosis-and-staging (accessed 19th July 2013)

10. http://www.who.int/respiratory/copd/burden/en/ (accessed on 19th July 2013)

11. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006; 28:523-32.

12. ICMR – MRC workshop on chronic diseases 2009.

13. R Prakash Upadhyay. An Overview of the Burden of Non-Communicable Diseases in India. Iranian J Publ Health, 2012;41:3,1-8.

14. Fishman's Pulmonary Diseases and Disorders, 4th edition, pgs 707-711, 731-745.

15. Dennis RJ, Maldonado D, Norman S, Baena E , Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. Chest 1996; 109: 115-119.

16. Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL. Long term particulate and other air pollutants and lung function in nonsmokers. Am J Respir Crit Care Med 1998;158:289-98.

17. Marc Decramer, Wim Janssens, Marc Miravitlles. Chronic obstructive pulmonary disease. Lancet 2012; 379: 1341–51.

18. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive Pulmonary disease. Lancet 2004; 364(9435): 709-21.

19. B.R. Celli, W. MacNee et al Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23: 932–946.

20. Lieke C. A. Christenhusz, Rilana Prenger, Marcel E. Pieterse, Erwin R. Seydel, Job van der Palen. Cost-effectiveness of an Intensive Smoking Cessation Intervention for COPD Outpatients. Nicotine Tob Res 2012; 14 (6):657-663.

21. Singh JM, Palda VA, Stanbrook MB, Chapman KR. Corticosteroid therapy for patients with acute exacerbations of

chronic obstructive pulmonary disease: a systematic review. Arch Intern Med. 2002; 162(22):2527-2536.

22. Anne. E Evensen. Management of COPD Exacerbations. Am Fam Physician. 2010;81(5):607-613, 616.

23. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease: the SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996; 154:959 –967.

24. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995; 274:1852–1857.

25. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:1298-303.

26. Rabe KF, Hurd S, Anzueto A, et al., for the Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive

pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-555.

27. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. Chest. 2001;119(4):1190-1209.

28. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(5):1608-1613.

29. 29. American Thoracic Society, European Respiratory Society Task Force. Standards for the Diagnosis and Management of Patients with COPD. Version 1.2 New York, NY:American Thoracic Society;2004. http://www.thoracic.org/go/copd.Accessed july19, 2013.

30. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities.Eur Respir J. 2006; 28: 1245 –57.

31. Linda Nici, Richard ZuWallack : Chronic Obstructive Pulmonary Disease Co- Morbidities and Systemic Consequences.

32. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M,

Rich S, Fishman A Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43(supplS):5S–12S

33. World Health Organization. Chronic cor pulmonale: a report of the expert committee. Circulation. 1963;27:594 –598.

34. Braunwald's Heart Disease,A Textbook of Cardiovascular Medicine, Ninth Edition

35. MeiLan K. Han, Vallerie V. McLaughlin, Gerard J. Criner, Fernando J. Martinez. Pulmonary Diseases and the Heart. Circulation. 2007;116:2992-3005

36. M. Malerba, G. Romanelli. Early cardiovascular involvement in Chronic Obstructive Pulmonary Disease. Monaldi Arch Chest Dis 2009; 71: 2, 59-65.

37. William MacNee, John Maclay, and David McAllister. Cardiovascular Injury and Repair in Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc. 2008;5:824–33.

38. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003; 107: 363-369.

39. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. Am J Respir Crit Care Med 1996; 154:1055–1060.

40. Curtis BM, O'Keefe JH. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. Mayo Clin Proc 2002;77:45–54.

PROFORMA:

CARDIAC TROPONIN T IN PATIENTS WITH ACUTE EXACERBATION OF COPD

Case No:

Name:

IP No:

Age:

Sex:

Address:

Occupation :

DOA :

DOD :

Tobacco Use :

Current smoker	Former smoker (> 1yr of abstinence)	Never

Chief Complaints:

Co Morbidities:

Co morbidity	Yes	No
Obesity		
Hypertension		
Diabetes mellitus		
IHD		
Previous MI		
Atrial fibrillation		

Significant past history:

Family history:

On examination:

Pallor	Icterus	Cyanosis	Clubbing	Lymphadeno	Pedal

Respiratory rate:

Heart rate:

Blood Pressure:

Temperature:

SpO_2 :

RS: Inspection:

Palpation:

Percussion:

Auscultation:

Rhonchi		
Crepitations		
Silent chest		
Other findings		

Other systems:

CVS:

Abdomen:

CNS:

Glasgow Coma Score:

<6	6 – 9	>9

Chest X Ray:

ECG:

ECHO:

ABG:

TC DC ESR

B. Urea Sr.Creatinine

Cardiac Troponin T :

On admission	24 Hrs later

PEFR:

Spirometry(dated) : FEV1/FVC =

Diagnosis:

Length of ICU stay:

No. of days on ventilator:

Hospital stay:

Outcome:

LIST OF ABBREVIATIONS USED

CAT: COPD assessment test

COPD: Chronic Obstructive Pulmonary Disease

CHF: Congestive Heart Failure

CRP: C-reactive protein

cTnT: Cardiac Troponin T

DM: Diabetes Mellitus

ECG: Electrocardiogram

ECHO: Echocardiography

FEV1: Forced Expiratory Volume in one second

FVC: Forced Vital Capacity

GCS: Glasgow Coma Scale

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HTN: Hypertension

HR: Heart Rate

ICU: Intensive Care Unit

IHD: Ischemic Heart Disease

LV: Left Ventricle

LVD: Left Ventricular Dysfunction

mMRC: modified Medical Research Council

NT-proBNP: N-terminal pro-brain natriuretic peptide

PH: Pulmonary Hypertension

$PaCO_2$: Partial Pressure of CO_2 in arterial blood

PaO2: Partial Pressure of Oxygen in arterial blood

PASP: Pulmonary Artery Systolic Pressure

MI: Myocardial Infarction

NIV: Non-invasive ventilation

RA: Right Atrium

RV: Right Ventricle

RR: Respiratory Rate

SBP: Systolic Blood Pressure

SD: Standard Deviation

SNS: Sympathetic Nervous System

WHO: World Health Organization

cTnT +Ve Master Chart

S.NO	AGE	SEX	SMOKE	Co-MOR	DURATION	R.RATE	PULSE	SPO2	Rh	CR	S	GCS	X-RAY	PASP mmHg	CHAMBERS
1	65	M	F	HT,DM	12	28	112	78	P	P	A	15	COPD	39	NORMAL
2	75	M	C	DM	10	30	106	60	P	P	A	15	COPD,LLZ	37	NORMAL
3	70	F	N	DM	7	34	110	82	P	A	P	15	COPD	35	RA,RVD
4	80	M	C	NIL	10	36	120	71	P	A	P	15	COPD	76	RA,RVD
5	60	M	C	NIL	4	34	104	78	P	P	A	15	COPD,BL	44	NORMAL
6	50	M	F	NIL	8	40	112	80	A	A	P	15	COPD	24	NORMAL
7	65	F	N	DM	5	32	110	56	P	P	A	6	COPD,LLZ	46	RA,RVD
8	56	M	C	NIL	5	38	134	76	P	A	P	7	COPD	60	RA,RVD
9	55	M	C	NIL	3	28	116	80	P	P	A	15	COPD.RLZ	46	RA,RVD
10	60	M	C	NIL	2	28	98	80	P	P	A	15	COPD	72	RA,RVD
11	60	M	F	NIL	5	32	112	76	P	P	A	15	COPD,RLZ	84	RA,RVD
12	65	M	F	HT	6	34	112	78	P	P	A	15	COPD,M	41	NORMAL
13	55	M	F	HT,DM	6	26	112	84	P	P	A	15	COPD,PHT	61	NORMAL
14	73	M	F	NIL	5	34	106	74	P	P	A	14	COPD	57	RA,RVD
15	65	M	F	HT	2	40	110	82	P	P	A	15	COPD	77	RA,RVD
16	73	M	F	HT	15	28	78	88	P	A	P	15	COPD,PHT	37	RA,RVD
17	68	M	C	NIL	6	24	82	40	A	P	P	4	COPD	27	RA,RVD
18	64	M	C	DM	6	30	106	82	P	P	A	15	COPD,RLZ	55	RA,RVD
19	60	M	C	HT,DM	5	28	118	80	P	A	A	15	COPD	36	NORMAL

S.NO	ECG	PaCO2	PaO2	cTnT(1)	cTnT(2)	PEFR	FEVI/FVC	VENTI	ICU	HOSP	OUTCOME
1	ST,P.PUL	26.5	66.9	0.01	0.3	<60	0.49	8	9	19	DISCHARGE
2	ST	33.5	46.7	0.01	0.19	80	0.53	0	5	8	DISCHARGE
3	ST	34.5	59.2	0.035	0.023	70	0.48	3	5	7	DISCHARGE
4	ST	48.3	59.3	0.026	0.014	70	0.57	3	3	4	DISCHARGE
5	ST	87.5	87.5	0.047	0.068	60	0.48	7	7	7	DISCHARGE
6	ST	74.9	33.4	0.22	0.051	60	0.04	3	4	4	DISCHARGE
7	ST	41.4	56.5	0.032	0.059	<60	0.52	4	6	10	DISCHARGE
8	ST,P.PUL	78.4	97.3	0.033	0.052	<60	UTP	4	4	4	DEATH
9	ST	58.2	47.7	0.022	0.01	<60	0.4	6	8	11	DISCHARGE
10	P.PUL	60.3	61	0.056	0.091	60	UTP	6	6	6	DEATH
11	RAD,P.PUL	27	62	0.27	0.01	60	0.6	5	6	12	DISCHARGE
12	ST	45	184.8	0.9	2.2	70	0.57	0	7	14	DISCHARGE
13	P.PUL	42.1	63.6	0.041	0.061	60	0.45	0	0	5	DISCHARGE
14	ST	38.6	55.3	0.59	0.44	60	0.56	4	4	4	DEATH
15	ST,P.PUL	26.4	59.1	0.4	0.2		0.54	5	6	15	DISCHARGE
16	RAD	54.3	57.3	1.2	0.58	60	UTP	3	9	15	DISCHARGE
17	NORMAL	115	214.9	0.022	0.021	<60	0.7	5	5	6	DISCHARGE
18	ST	79.7	96	0.09	0.022	<60	0.36	3	4	11	DISCHARGE
19	ST	68.6	74.9	0.16	1.1	<60	0.58	0	2	8	DISCHARGE

cTnT –ve Master Chart

S.NO	AGE	SEX	SMOKE	Co-MOR	DURATION	R.RATE	PULSE	SPO2	Rh	CR	S	GCS	X-RAY	PASP mmHg	CHAMBERS
1	56	M	C	NIL	2	36	130	78	P	A	P	15	COPD	37	NORMAL
2	65	M	C	NIL	4	30	114	82	P	P	A	15	COPD,RL	60	RA,RVD
3	62	M	C	NIL	5	32	96	82	P	A	A	15	COPD	36	NORMAL
4	55	M	C	NIL	2	30	120	78	P	P	A	15	COPD,LLZ	37	NORMAL
5	56	M	F	NIL	5	32	102	84	P	A	A	15	COPD	36	NORMAL
6	70	M	F	NIL	3	28	96	88	P	P	A	15	COPD	46	NORMAL
7	80	M	F	NIL	3	24	90	84	P	A	A	15	COPD	36	NORMAL
8	73	F	F	NIL	3	26	100	90	P	P	A	15	COPD	56	RA,RVD
9	75	M	N	HT	5	40	96	70	P	P	A	8	COPD,RLZ	38	RA,RVD
10	80	M	C	NIL	3	26	88	80	P	P	A	15	COPD,MZ	60	NORMAL
11	66	M	C	NIL	10	38	100	82	P	P	A	15	COPD,LLZ	36	NORMAL
12	65	M	C	DM,HT	2	36	102	80	A	A	P	15	COPD,RLZ	24	NORMAL
13	65	M	C	NIL	2	22	90	86	P	P	A	15	COPD	36	NORMAL
14	70	M	C	HT	2	36	94	84	P	A	A	15	COPD	37	NORMAL

15	60	M	F	NIL	5	34	94	82	P	P	A	13	COPD	70	RA,RVD
16	65	M	C	NIL	3	40	106	80	P	A	A	5	COPD	36	NORMAL
17	64	M	C	NIL	2	30	120	80	P	P	A	15	COPD	36	NORMAL
18	60	F	C	NIL	5	32	108	78	P	A	P	15	COPD,PHT	56	RA,RVD
19	65	M	N	OBESITY	4	28	106	79	P	P	A	15	COPD	45	RA,RVD
20	68	M	C	NIL	6	24	98	86	P	P	A	15	COPD	28	NORMAL
21	55	M	C	HT,DM	4	32	130	85	P	P	A	15	COPD	43	NORMAL
22	65	M	C	HT,DM	4	26	100	80	P	P	A	15	COPD,B/L	60	RA,RVD
23	60	M	F	HT,DM	2	26	98	88	P	P	A	15	COPD	32	LVH
24	77	M	F	HT,DM	3	30	130	88	P	P	A	15	COPD	45	ASH
25	65	M	C	DM	5	36	112	84	P	P	A	15	COPD	47	RA,RVD
26	70	M	C	NIL	3	28	96	86	P	A	A	15	COPD	60	RA,RVD
27	70	M	C	NIL	5	26	100	90	P	A	A	15	COPD	49	NORMAL
28	60	M	F	NIL	9	32	110	69	P	P	A	15	COPD	70	RA,RVD
29	95	M	C	NIL	6	24	98	80	P	A	P	11	COPD,PHT	40	NORMAL
30	60	M	F	NIL	3	30	104	84	P	A	A	15	COPD	30	NORMAL
31	73	M	C	NIL	3	26	94	84	P	A	A	15	COPD	40	NORMAL

S.NO	ECG	PaCO2	PaO2	cTnT(1)	cTnT(2)	PEFR	FEVI/FVC	VENTI	ICU	HOSP	OUTCOME
1	ST,P.PUL	27	91	<0.01	<0.01	60	0.5	0	0	3	DISCHARGE
2	ST,P.PUL	53	34	<0.01	<0.01	60	0.5	4	5	6	DISCHARGE
3	ST,P.PUL	50	56	<0.01	<0.01	60	0.3	0	0	5	DISCHARGE
4	ST	25	60	<0.01	<0.01	80	0.7	0	0	5	DISCHARGE
5	ST,P.PUL	33	78	0.01	0	100	0.5	4	4	7	DISCHARGE
6	ST	27	53	<0.01	<0.01	60	0.4	0	0	4	DISCHARGE
7	NORMAL	50	72	<0.01	<0.01	70	0.6	4	5	7	DISCHARGE
8	ST,P.PUL	41	39	<0.01	<0.01	80	0.4	0	0	3	DISCHARGE
9	P.PUL	42	75	0.014	0	NA	NA	4	4	4	DEATH
10	ST,P.PUL	26	61	<0.01	<0.01	60	0.5	5	5	9	DISCHARGE
11	ST	34	65	<0.01	<0.01	60	NA	8	9	9	DEATH
12	ST	38	58	<0.01	<0.01	NA	NA	25	25	25	DISCHARGE
13	NORMAL	40	50	<0.01	<0.01	120	0.5	0	0	5	DISCHARGE
14	ST,P.PUL	30	66	<0.01	<0.01	100	0.5	0	0	4	DISCHARGE
15	ST,P.PUL	52	72	<0.01	0	90	0.6	3	3	5	DISCHARGE
16	ST	37	50	<0.01	<0.01	100	0.4	0	0	5	DISCHARGE
17	ST	27	58	0.016	<0.01	70	0.6	0	0	4	DISCHARGE
18	ST,RAD	52	67	<0.01	<0.01	60	0.6	3	3	6	DISCHARGE
19	ST,RAD	59	77	<0.01	<0.01	<60	0.6	0	3	5	DISCHARGE

20	ST	51	68	<0.01	<0.01	70	0.7	0	0	4	DISCHARGE
21	ST,P.PUL	41	63	<0.01	<0.01	60	0.6	0	0	5	DISCHARGE
22	INV V4-V6	59	45	<0.01	<0.01	60	0.5	0	2	4	DISCHARGE
23	NORMAL	26	79	<0.01	<0.01	70	NA	0	0	3	DISCHARGE
24	ST,LAD	28	63	<0.01	<0.01	80	NA	0	5	6	DISCHARGE
25	ST,RAD	45	68	<0.01	<0.01	70	0.6	0	6	7	DISCHARGE
26	ST,RAD	60	88	<0.01	<0.01	70	0.4	4	4	7	DISCHARGE
27	ST	39	86	<0.10	<0.01	NA	NA	4	5	7	DISCHARGE
28	RAD,MAT	61	97	0.015	0	<60	0.6	0	0	3	DISCHARGE
29	ST	61	88	<0.01	<0.01	70	0.4	1	1	4	DISCHARGE
30	ST,P.PUL	47	87	<0.01	<0.01	70	0.4	0	0	5	DISCHARGE
31	ST	55	89	<0.01	<0.01	65	0.7	0	0	4	DISCHARGE

KEY TO MASTER CHART:

C- current smoker

F- former smoker

N- non smoker

M- Male

F- Female

B - breathlessness

C&E - cough and expectoration

E- pedal edema

HTN- hypertension

DM- diabetes mellitus

RR- Respiratory rate

HR- heart rate

SBP- systolic BP

Rh- rhonchi

CR- crepitations

S- silent chest

R- Right

L- Left

UZ- Upper Aone

Lz- Lower Zone

Con- Consolidation

PH- Pulmonary Hypertension

RA - right atrium

RV- right ventricle

DIL – dilated

ST - sinus tachycardia

P.pul- P. pulmonale

RAD - Right axis deviation

UTP - Unable to Perform

NIV - Non invasive Ventilation

Ref.No.8102/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 09.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for September 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on September 12th 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the Ethical Committee

Name of P.G.	Course	Name of the Project	Remarks
Dr.P.Sathiya saisudhagar@gmail.com	PG in MD (General Medicine) Madurai Medical College and Govt. Rajaji Hospital, Madurai.	**A study of cardiac troponin T-in acute exacerbation of chronic obstructive pulmonary disease.**	**Approved**

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical Committee

24.9.14.

DEAN/Convenor
Madurai Medical College &
Govt. Rajaji Hospital, Madurai.

20/9/14

To
The above Applicant
-thro. Head of the Department concerned

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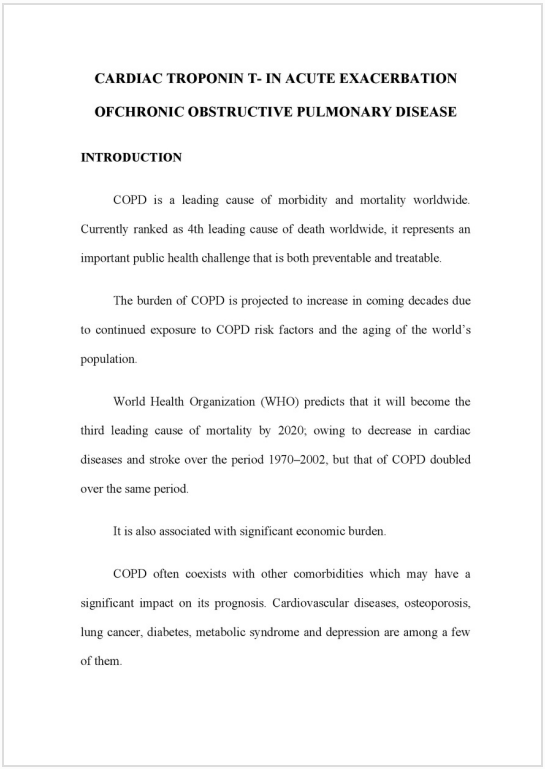


CARDIAC TROPONIN T- IN ACUTE EXACERBATION OFCHRONIC OBSTRUCTIVE PULMONARY DISEASE

INTRODUCTION

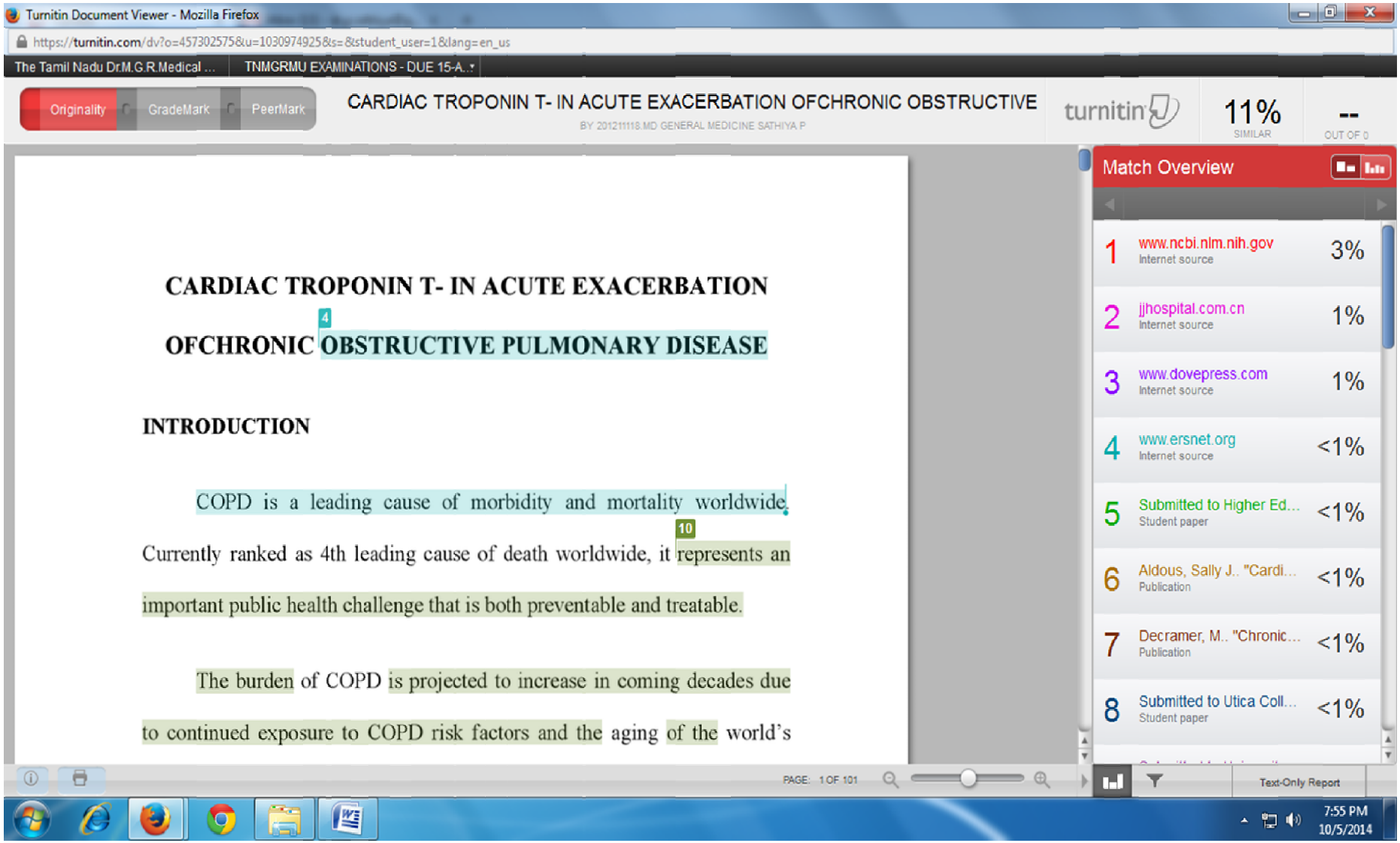
COPD is a leading cause of morbidity and mortality worldwide. Currently ranked as 4th leading cause of death worldwide, it represents an important public health challenge that is both preventable and treatable.

The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.

World Health Organization (WHO) predicts that it will become the third leading cause of mortality by 2020; owing to decrease in cardiac diseases and stroke over the period 1970–2002, but that of COPD doubled over the same period.

It is also associated with significant economic burden.

COPD often coexists with other comorbidities which may have a significant impact on its prognosis. Cardiovascular diseases, osteoporosis, lung cancer, diabetes, metabolic syndrome and depression are among a few of them.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CARDIAC TROPONIN T- IN ACUTE EXACERBATION
OFCHRONIC OBSTRUCTIVE PULMONARY DISEASE
INTRODUCTION
COPD is a leading cause of morbidity and mortality worldwide.
Currently ranked as 4th leading cause of death worldwide, it represents an
important public health challenge that is both preventable and treatable.
The burden of COPD is projected to increase in coming decades due
to continued exposure to COPD risk factors and the aging of the world's
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