A STUDY ON ECHOCARDIOGRAPHIC PROFILE OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DISSERTATION SUBMITTED

BY

DR. S. MANOJ KUMAR

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE (M.D)

IN

TUBERCULOSIS AND RESPIRATORY DISEASES

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

UNDER THE GUIDANCE OF

DR. K. ANUPAMA MURTHY, MD (CHEST)

APRIL 2015

DEPARTMENT OF RESPIRATORY MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

COIMBATORE

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I wholeheartedly thank my professor and head, **DR. K. ANUPAMA MURTHY** for guiding me throughout the study with her vast experience, timely suggestions and correcting all mistakes which I have committed. She has been a great source of motivation in all my difficult times encountered during my residentship.With her endless enthusiasm and patience, she was the cornerstone in successfully completing my dissertation.

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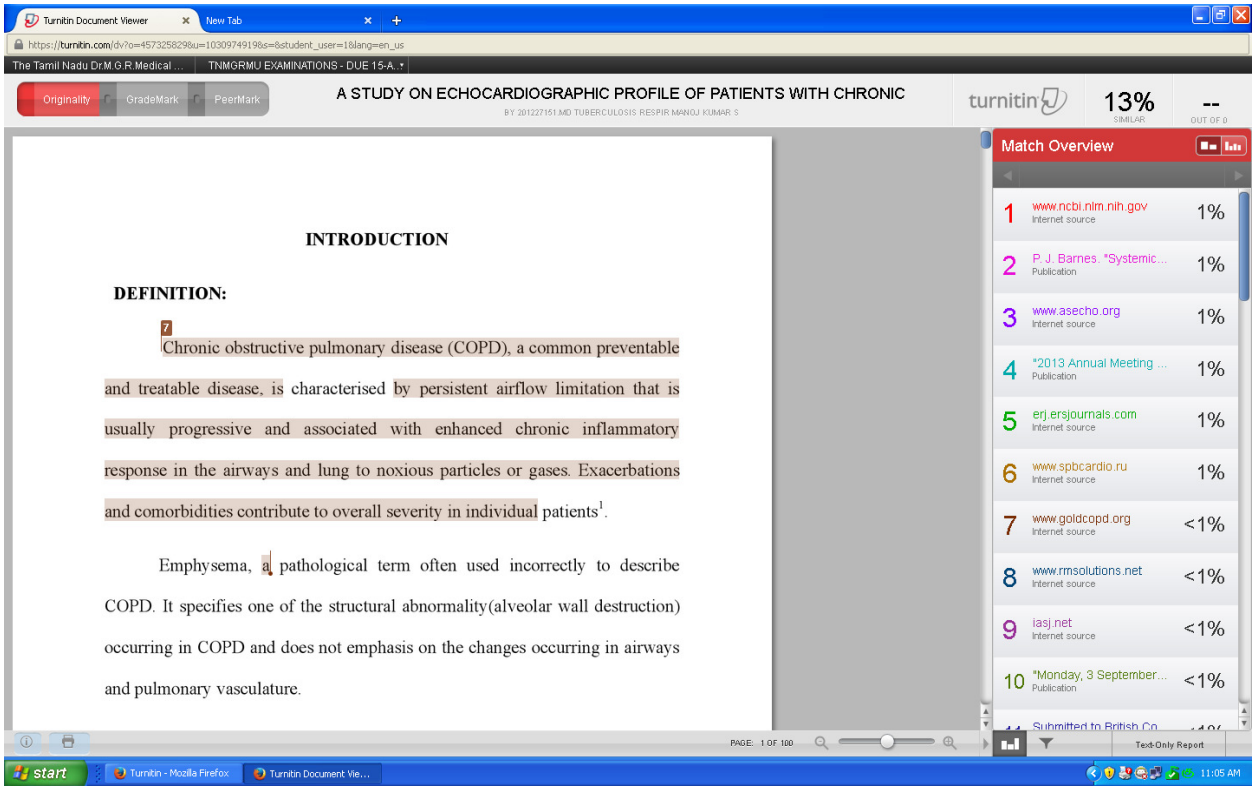
I wish to dedicate this work to my family for their unending love.

PLAGIARISM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INTRODUCTION
DEFINITION:
Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lung to noxious particles or gases. Exacerbations and comorbidities contribute to overall severity in individual patients[1].
Emphysema, a pathological term often used incorrectly to describe COPD. It specifies one of the structural abnormality(alveolar wall destruction) occurring in COPD and does not emphasis on the changes occurring in airways and pulmonary vasculature.
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May 3, 2013

To
Dr S Manoj Kumar
Postgraduate
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The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 18th April, 2013 in its expedited review meeting held at College Council Room, PSG IMS&R, between 1.30 pm and 2.30 pm, and discussed your study proposal entitled:

"A study on echocardiographic profile of patients with chronic obstructive pulmonary disease" under the guidance of Dr Anupama Murthy, Dr R Karthikeyan and Dr G Rajendiran

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Confidentiality statement
4. Application for waiver of consent
5. Data Collection Tool
6. CV
7. Budget

After due consideration, the Committee has decided to approve the above study proposal.

The members who attended the meeting, at which your study proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member – Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member – Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member – Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The approval is valid for one year.

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We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

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Yours truly,

3.5.13

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

SECRETARY
PSG IMS & R
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INSTITUTIONAL HUMAN ETHICS COMMITTEE

CONTENTS

ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
PH	Pulmonary Hypertension
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MMRC	Modified Medical Research Council
BMI	Body Mass Index
FVC	Forced Vital Capacity
FEV 1	Forced Expiratory Volume (1st second)
FEV1/FVC	Forced Expiratory Volume (1st second) /Forced Vital Capacity.
6MWD	Six Minute Walk Distance
SPAP	Systolic Pulmonary artery pressure
RVSP	Right Ventricular Systolic Pressure
LVDD	Left Ventricle Diastolic Dysfunction
RVID	Right Ventricle Internal Diameter
EF	Ejection Fraction
RVT	Right Ventricle Thickness
TAPSE	Tricuspid Annular Plane Systolic Excursion
TR	Tricuspid Regurgitation
IVC	Inferior Vena Cava
LVEI	Left Ventricle Eccentricity Index
LVIDs	Left Ventricle Internal Diameter in systole
LVIDd	Left Ventricle Internal Diameter in diastole

ABSTRACT

A study on echocardiographic profile of patients with chronic obstructive pulmonary disease.

S .Manoj kumar, K.Anupama Murthy, R.Karthikeyan, G.Rajendiran, P.Arun kumar

Department of Respiratory medicine, Cardiology; PSG Hospitals, Coimbatore, Tamil Nadu, India

- Background:

  Chronic obstructive pulmonary disease (COPD) is a systemic disease with various extrapulmonary manifestations. Cardiovascular disease is a major comorbidity in COPD and probably the most frequent and most important disease co existing with COPD. Echocardiography is one of the simplest and non invasive tool in assessing the cardiac status.

- Aim of the Study:

  To evaluate the clinico-physiological characteristics of copd and correlate them with the echocardiographic findings and to identify the predictors of pulmonary hypertension in COPD patients.

- Materials and methods:

  Forty COPD patients diagnosed by GOLD criteria who neither has other lung disease which alters spirometry nor has primary cardiac disease were recruited. They were explained about the study and interviewed for socio demographic details. They were subjected for thorough clinical examination and followed by Echocardiography.

- Results:

  The frequency of mild, moderate, severe and very severe COPD were 7.5%, 42.5%, 37.5%, 12.5% respectively.Pulmonary hypertension(PH) defined as systolic pulmonary artery pressure (sPAP) > 30 mmHg was found in 35%(n= 14) of study subjects. None of them had s PAP > 50 mmHg. PH was present in 26.7%, 35.3% and 60% of moderate, severe and very severe COPD patients. The occurrence of PH increased with severity of COPD. None of the patients had RV systolic dysfunction documented by TAPSE with mean of 1.96±0.134. RV Hypertrophy based on RV Thickness was present irrespective of PH with mean of 0.68±0.13. LV Diastolic Dysfunction was present in 35%(n=14) of study population. By multivariate logistic regression analysis, BMI showed significant correlation with PH(

adjusted odd's ratio of 0.76, 95% confidence interval 0.59 – 0.98, P'=0.04) Duration of disease, 6MWD, LVDD does not correlate with PH.

- Conclusion:

  Our study showed that prevalence of pulmonary hypertension increased with severity of COPD. Severe pulmonary hypertension was not observed in our study with stable COPD patients. Right ventricle hypertrophy and diastolic dysfunction of left ventricle were the other common findings in COPD patients. We found that patients with low BMI have 24% less chance for developing pulmonary hypertension. Since cardiovascular disease is the major cause of morbidity and mortality in COPD, it is essential to evaluate the cardiac status at the time of initial diagnosis. The overall survival and quality of life can be improved by addressing this comorbidity.

INTRODUCTION

DEFINITION:

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lung to noxious particles or gases. Exacerbations and comorbidities contribute to overall severity in individual patients[1].

Emphysema, a pathological term often used incorrectly to describe COPD. It specifies one of the structural abnormality(alveolar wall destruction) occurring in COPD and does not emphasis on the changes occurring in airways and pulmonary vasculature.

Chronic bronchitis is a clinical diagnosis described as production of sputum for minimum of three months in 2 successive years. The airflow limitation may follow or precede it, So spirometry can be normal.

EPIDEMIOLOGY:

The prevalence of COPD according to PLATINO (Latin American Project for the Investigation of Obstructive Lung Disease) study was 7.8% in Mexico , as high as 19.7% in Uruguay[2].The prevalence of COPD estimated by BOLD(Burden of obstructive lung disease program) among non smokers were 3

% to 11%[3]. Death due to COPD was ranked to be fifth in 2002. In the next ten years, COPD deaths will increase by atleast one third. In 2030, the third major etiology for death worldwide will be COPD[4].

The reported prevalence rate from the asian countries were lower than the western world. In twelve Asia Pacific countries, the study by Tan et al point to the contrary and noted 6.3 % of combined prevalance. The above mentioned prevalence was two times higher than the total prevalance of 3.8 % depicted by World Health organisation[88]. Several small surveys based on unvalidated questionnaire-interviews depicted 2 %to 22 % of COPD prevalence among males and 1.2 % to 19 % COPD prevalence among females, which enormously varied in their methodology and could not be relied for national assessment[89]. INSEARCH - The Indian study on Epidemiology of Asthma, Respiratory symptoms and Chronic bronchitis was aided by the Indian Council of Medical Research (ICMR) to study the epidemiology of chronic respiratory diseases. The first Phase of the study was done in four areas and the second phase was carried out in twelve places. The first phase results from Bangalore, Chandigarh, Kanpur, Delhi showed 5.0 % prevalence in males and the female prevalence was 3.2 % [87].

The burden of COPD during 1971 was about 6.45 million. In 2011 it increased to 14.84 million. The rise in population is one of the important reason for such high burden. Among Indians, COPD is high in men

and smokers. The increased male prevalence is because of male : female differences in smoking habits[86,87]. The male : female COPD ratio and the smoker : nonsmoker ratio are not as high as in the Westernpopulations[86,87]. This is due to increased exposure of fumes among females, especially in the rural and hilly areas, on combustion of wood for heating ,cooking[90]. In non smoking women, exposure to environmental tobacco smoke is a significant risk factor. Certain geographical and regional difference exists in COPD occurence . Earlier, COPD was said to be more common in North India[88].The distribution of chronic obstructive pulmonary disease in each state has not been studied extensively. The INSEARCH data are from specific areas of various states. So, the prevalence in each state cannot be estimated from the above data. According to Health Resource Centre in Maharastra, major cause of mortality is COPD [91].

Airway obstruction is an important cause of dyspnoea on exertion. It gradually worsens to limit the routine activities and an important cause of work loss. Among non-communicable diseases, loss of 3 % DALY is due to COPD[92]. Stable COPD may get worsened due to comorbidities like Bullae and pneumothorax . Pulmonary thromboembolism, hyperuricaemia, hyperviscosity secondary to polycythemia and long standing hypoxia are the other abnormalities in COPD . The presenting symptom in thromboembolism vary depending upon the level of obstruction in the vessel.

In 1988, a residential survey carried out in rural areas, estimated 0.57 million COPD deaths . According to this limited death statistics, among the

non-communicable diseases, the major cause of mortality is chronic obstructive pulmonary disease next to the deaths reported due to trauma. The survey from varied resources in rural India (NFHSI I , II ; Mortality survey, Registrar General of India's yearly manual, 2001 Indian census, various field studies) , point asthma, bronchitis as the major cause of mortality in men and women[93]. The amount spent on smoking related materials was around Rs.1340 yearly, Rs. 11454 as indirect losses annually, according to an ICMR study in 1998. The costs reflected 30 percentage of the individual's income as financial Burden[94].

RISK FACTORS:

Evidence are not from cause effect relation, but from the epidemiological cross sectional studies . No study has included pre/perinatal period. Gene environment interaction plays a major role and link in complex ways. Cigarette smoking is a well known risk factor for COPD. WHO report states that around 15 billion cigarettes are smoked daily throughout the world[4] .COPD was more common in males as a result of smoking pattern. Both in high-income countries due to tobacco use and in low-income countries due to indoor pollution (biomass for cooking and heating), the prevalence of disease among women is on the rise[1]. Genetic factors like alpha one antitrypsin deficiency, low birth weight, occupational exposure to fumes, ageing, outdoor air pollution, poor socioeconomic status [5,6,7] are the other major risk factors.

GENETIC FACTORS:

Alpha 1 antitrypsin deficiency, mmp12, hedge hog, Alpha nicotinic choline receptor are the major genes linked with COPD. Pi ZZ - homozygosity for the Z allele, is associated with severe α1-AT deficiency (less than 15 percent of normal). Its incidence is about 1 in 3000 people in united states and rare among Asians, African Americans. The Z allele of α1-AT shows slower association with neutrophil elastase than the association of normal α1-AT . So the persons with Pi Z phenotype have a deficient α1-AT protein and less efficient α1-AT than normal α1-AT. Majority of individuals present with respiratory symptoms, some have evidence of liver disease and small percentage have rare clinical manifestations such as panniculitis. Some cases are detected from screening for α1-AT deficiency prompted by finding the deficiency in a family member. Smoking is highly deleterious and hastens the development of COPD in most people with the deficiency. The typical Pi Z individual who smokes has respiratory symptoms by age 40, about 15 years earlier than equally deficient individuals who have never smoked. Some individuals with PiZ, present with respiratory symptoms only in advanced age .

AGE & GENDER:

Healthy aging as such leading to COPD is unclear. It may be due to cumulative risk exposure. In developed nations, prevalence almost equal in both sex. Women are more susceptible to the effects of smoke.

LUNG DEVELOPMENT:

FEV1 in adulthood has positive correlation with birth weight. Recurrent childhood respiratory infections will have negative impact on lung function .Childhood disadvantage factors are as important as smoking .

SOCIO ECONOMIC STATUS:

People belonging to low socioeconomic status had documented to have reduced lung function than the high socioeconomic status. Malnutrition, indoor pollution, infection and over crowding were the proposed mechanism.

TUBERCULOSIS AND HIV:

Post Pulmonary tuberculosis changes like bronchiectasis, fibrotic changes of airway were also well known etiology for COPD. HIV infection accelerate smoking related emphysema.

FAMILY HISTORY:

Significant airflow obstruction has been documented in smoking siblings of COPD patients. Individuals with history of airway hyperreactivity and family history of asthma were at high risk of developing COPD.

DIAGNOSIS OF COPD:

A diagnosis of chronic obstructive pulmonary disease must be considered in an individual presenting with complaints of breathlessness on physical activity, cough which is chronic and associated with expectoration of sputum , with background exposure to risk factors. The other symptoms like chest tightness, wheeze are non specific. In patients with severe, very severe obstruction symptoms like fatigue, anorexia which are regarded as co morbidities. Patients who developed corpulmonale have swelling of feet, abdominal distention and decreased urine output. Patient may have syncope secondary to cough. Rib fractures are not uncommon in COPD. In advanced stages, clinical examination show the features of hyperinflation of lungs like reduced breath sounds , diaphragm at low level, percussion revealing hyper resonant note and a distance of 4 cm or below when measured between thyroid and cricoid cartilages. Spirometry should be performed to establish the airflow obstruction. The post bronchodilator FEV1/FVC ratio lower than 0.70 documents the presence of airway obstruction.Based on GOLD criteria, they are classified as mild, moderate, severe, very severe disease based on post bronchodilator spirometric FEV1 >80%, FEV1 <80% to >50%, FEV1 <50% to 30%, FEV1 <30% respectively.

The assessment of COPD should also include the severity of symptoms, especially dyspnoea, according to modified medical research council grade or

by using COPD Assessment Test questionnaire. The previous history of exacerbation or hospitalization should also be considered during assessment of COPD .Chest xray show hyperinflated lung parenchyma, flat diaphragm, tubular heart, widened intercostal space. HRCT Thorax may show the emphysematous changes and in some patients bulla can be visualized. It helps to rule out the other coexisting diseases like interstitial lung disease, bronchiectasis. Lung volume measurements by helium dilution, body plethysmography, single breath method or nitrogen washout technique can help in determining residual volume and total lung capacity which cannot be measured by spirometry. Diffusion capacity by carbon monoxide inversely correlates with emphysema.

Differential diagnosis of emphysema:

1. Air trapping in acute asthma
2. Obstructive hyperinflation
3. Compensatory hyperinflation
4. Congenital lobar hyperinflation
5. Ductectasia
6. Swyer James syndrome

Differential diagnosis for lesion in large airways:

1. Chronic bronchitis

2. Bronchiectasis
3. Asthma
4. Relapsing polychondritis
5. Tracheomegaly
6. Tracheobronchiopathica osteoplastica

Differential diagnosis for lesion in small airways of COPD:

1. Asthma
2. Constrictive bronchiolitis
3. Follicular bronchiolitis
4. Proliferative bronchiolitis
5. Panbronchiolitis

PROGNOSIS:

Morbidity and mortality in COPD are influenced by various factors. COPD patients with low Body mass index, low exercise capacity assessed by six minute walk test, decreased FEV1, low DLCO, comorbidities, recurrent exacerbations, poor health related quality of life, resting tachycardia, corpulmonale, hypoxemia, active smoking were shown to have poor prognosis. COPD patients with forced expiratory volume in first second value of less than 35% of predicted have a mortality of around 10% every year. According to BODE index, the two year mortality for a patient with score more than 7 is

30%, for those with a score 5-6 have a 15% mortality and patients with score less than 5 have a better prognosis with a predicted two year mortality of 10%.

PREVENTION OF DISEASE PROGRESSION:

COPD patients have progressive decline in pulmonary function even with treatment. This deterioration in pulmonary function is rapid in actively smoking patients. Smoking cessation helps to avoid the fast decline in lung function. Occupational exposure to fumes, irritant would alter the lung function. They are educated to use respiratory protective devices. COPD patients should be immunized with influenza vaccine every year. The progression can be halted in patients with COPD due to alpha 1 anti trypsin deficiency by administering alpha one anti trypsin extract derived from plasma of humans. A dose of 60 mg per week by intravenous administration is recommended. The benefit will be more for moderate COPD patients. To prevent the deconditioning of muscle, COPD patients are encouraged to undergo self directed physical activity. They should be motivated to do aerobic low intensity physical activity for a minimum period of twenty minutes atleast thrice weekly. COPD patients who have breathlessness of grade 2 MMRC should be encouraged to participate in rehabilitation program .The importance of nutrition and nature of the disease state should be emphasized.

COPD AND SYSTEMIC MANIFESTATIONS:

There are plenty of evidence indicating chronic obstructive pulmonary disease as a complex disease with various systemic manifestations. These systemic manifestations occur due to the release of cytokines like Tumor necrosis factor alpha, Interleukin 1β, chemokines, Interleukin 6; Acute phase reactants like Fibrinogen, C-Reactive Protein(CRP), Surfactant D, Serum Amyloid A; Circulating cells like lymphocytes, monocytes and natural killer cells[10,11].

The comorbidities linked with COPD are cardiovascular diseases, metabolic syndrome, osteoporosis, depression, lung malignancy, skeletal muscle dysfunction, normocytic anemia, obstructive sleep apnoea[1](Table 1)

The different views relating Chronic obstructive pulmonary disease with its manifestation and comorbidities are

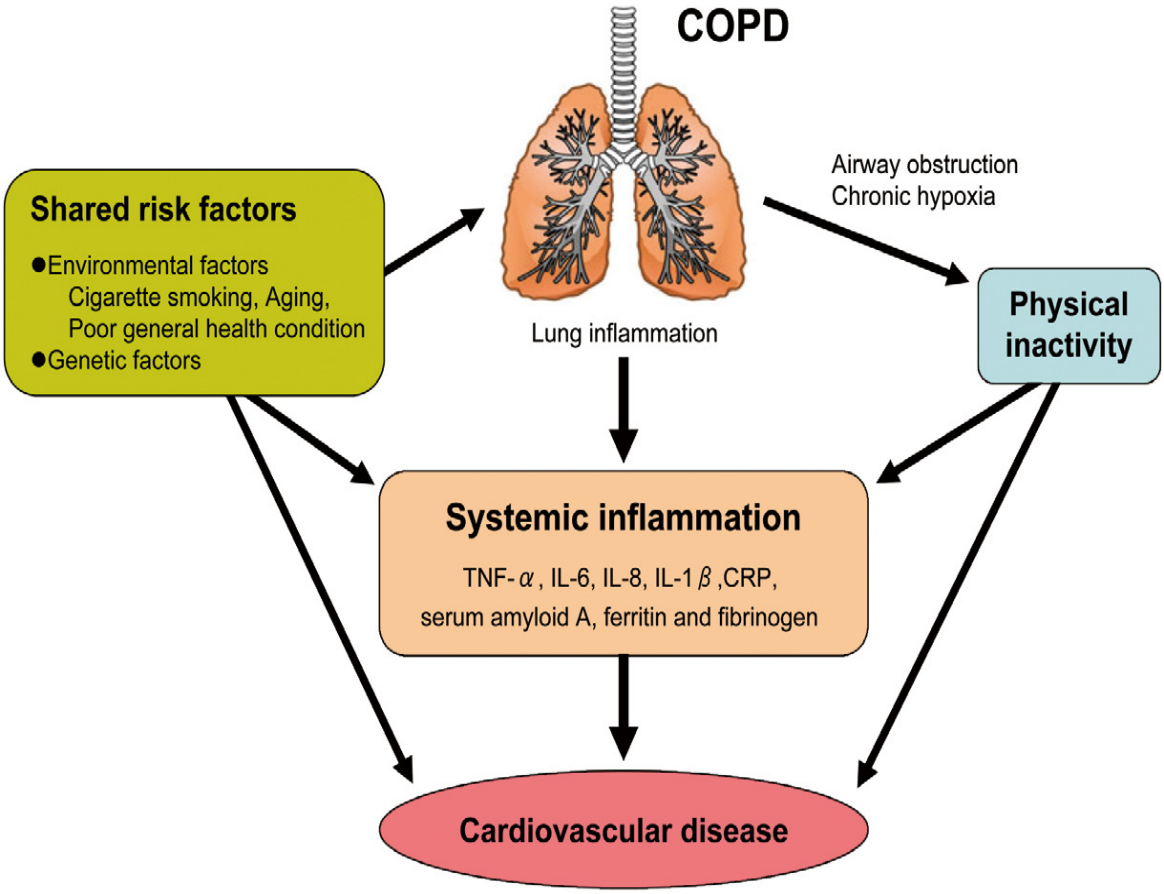
1. Systemic manifestations occur as a result of ‘‘ direct spill over’’ of the inflammatory pathways taking place in the lungs of COPD patients.
2. Systemic inflammation also occurs due to release of mediators like IL-6 in tissue hypoxia, increased 1L -8, TNF α, IL - 1β in hyperinflation of lungs, muscle dysfunction, bone marrow stimulation.
3. Increased oxidative stress due to reactive oxygen species(ROS) especially oxygen radicals.
4. Aging with shortened telomere length is a cause for systemic inflammation as a result of release of 1L -6, TNF α by senescent cells.

5. The pulmonary manifestations in COPD are another form of expression of a systemic inflammation with various organ compromise [8,9].

Table- 1 Chronic obstructive pulmonary disease and Systemic manifestations.

Coronary artery disease
Arrhythmia
Congestive cardiac failure
Systemic hypertension
Pulmonary hypertension
Cerebrovascular disease
Peripheral vascular disease
Obstructive sleep apnoea
Diabetes
Metabolic syndrome
Skeletal muscle wasting
Lung cancer
Anxiety
Depression
Osteoporosis
Normocytic anaemia
Cachexia

Figure 1. Mechanism underlying the association between chronic obstructive pulmonary disease (COPD) and cardiovascular disease.



CARDIOVASCULAR DISEASE:

The lungs and the heart have an anatomical and functional relation, any altered function in one of the organs will have an impact on the other. This is of paramount importance in COPD individuals which is explained by the following associations.

1. Pathologies sharing similar risks - cigarette smoking is a common risk factor for disease in coronary artery (CAD), congestive cardiac failure(CCF), COPD.

2. Presence of minimal level of systemic inflammation
3. Physical inactivity
4. Activation of sympathetic nervous system – high resting heart rate, reduced heart rate variability.
5. Increased arterial stiffness measured by pulse wave velocity(PWV).
6. Altered cardiac function from primary pulmonary disease like secondary pulmonary hypertension , decreased ventricular function due to increased intra thoracic mechanical loads.

Cardiovascular disease is the most important comorbidity in COPD patients. The major cardiac manifestations are ischemic heart disease, cardiac failure, arrhythmia, systemic hypertension and pulmonary hypertension. In mild and moderate COPD, the major cause of mortality are the cardiac complications.

COPD AND CORONARY ARTERY DISEASE:

COPD and CAD have common risk factors like exposure to cigarette smoke, sedentary life style and old age. Patients with airflow obstruction were prone to death from myocardial infarction which is independent of smoking history, age, sex. The Lung Health Trial, followed 6,000 COPD patients for 14 yrs, found FEV1 as an independent factor for predicting the probability of mortality from myocardial infarction. The above risk persists even after allowing for smoking. COPD patients with mild obstruction have a higher mortality from cardiac etiology than from pulmonary cause per se. The factors

linked with the COPD and atherosclerotic disease overlap each other . Mannino did a population based study and showed individuals with very severe obstruction had a two fold greater risk of cardiovascular disease, higher risk of hospitalization and a 1.6 times increased prevalence of hypertension[74]. The occurrence of minimal systemic inflammatory changes could be the possible event driving both COPD and atherosclerotic cardiovascular disease . The systemic inflammatory mediators in COPD has been proposed in the genesis of coronary heart disease and atherosclerosis. The increased amount of macrophages, Interferon secreting Th1 lymphocytes are present in peripheral lungs of COPD and atherosclerotic plaques.

COPD AND HEART FAILURE:

The dynamic hyperinflation and increased intra thoracic pressure swings auguments the mechanical load on cardiac chambers. Rutten found left ventricular dysfunction of 20% among COPD patients[75]. The overlap in symptoms and signs complicate the diagnosis of heart failure in COPD. Cardiac failure in COPD patients can be differentiated by measuring B type natriuretic peptide, N terminal prohormone brain natriuretic peptide (NT-proBNP). NTproBNP when elevated in COPD patients has been shown to correlate with decreased physical activity, suggesting that left ventricular dysfunction contributes exercise limitation. It is shown that if the heart dimension is reduced in patients with emphysema, the actual volume of

intra thoracic blood is also decreased. After lung volume reduction surgery, intra thoracic blood volume increases in patients with hyperinflation.

This improved left ventricular function after the alteration in intra thoracic pressures makes the concept of systemic inflammation implicated in causing heart failure debatable.

ARTERIAL STIFFNESS AND ENDOTHELIAL FUNCTION:

Arterial stiffness, one of the predictor of cardiovascular events can be computed noninvasively by radial artery tonometry or calculating aortic pulse wave velocity. Stiffness of artery is increased in COPD patients than the normal smokers and nonsmokers Arterial stiffness is neither related to severity of disease nor circulating amount of C Reactive protein. This increased arterial stiffness predispose to high risk of cardiovascular disease and systemic hypertension. Arterial stiffness depict common pathological mechanisms like connective tissue abnormalities and systemic inflammation. The possible mechanism for decreased arterial stiffness is impaired release of endothelial nitric oxide. Patients having emphysema show decreased flow mediated vasodilatation reflecting impairment in function of endothelium due to systemic inflammatory markers.

PULMONARY HYPERTENSION:

Impaired endothelial function as a result of endothelial injury by cigarette smoke products and decreased endothelial expression of nitric oxide, prostacyclin synthase are being proposed as the initial mechanism in the natural

pathway of pulmonary hypertension in COPD[12] . During the course of disease, sustained hypoxemia and inflammation induce vascular remodeling[13].

Measuring pulmonary artery pressure by right heart catheterisation has been the gold standard technique. Due to invasive nature of the procedure and associated complications, it is not routinely performed. The estimate of pulmonary artery pressure by echocardiography has been shown to have good correlation to that of invasive measurement. Moreover echocardiography is non invasive tool, simple to perform, cost effective. It also helps to measure various parameters like ejection fraction, dimensions of chambers, valve functions. So, echocardiography can be used as a screening tool in assessing the cardiac status.

In mild and moderate COPD, clinically significant pulmonary hypertension at rest is rare but can develop during exercise. Very severe COPD patients undergoing lung transplantation or lung volume reduction surgery (LVRS) have been documented to have moderate to severe PHT in about 50% of cases [15]. There are group of COPD patients(1 to 3%) having PHT disproportionate to the degree of airway obstruction [14]. Thus varying prevalence of pulmonary hypertension had been demonstrated in different studies. Some studies included patients with exacerbation. COPD patients at the time of exacerbation will have increased pulmonary pressure when compared to the stable nature of the disease. Pulmonary hypertension corpulmonale are independent risk factors in predicting morbidity, mortality in patients with chronic obstructive pulmonary

disease. The presence of severe pulmonary hypertension in patients with COPD, needs further work up to exclude coexisting disease. The presence of pulmonary hypertension in COPD patients had poor survival rate. The 5 year survival rate for mild , moderate and severe pulmonary hypertension were 50% , 30% and 0 % respectively. Varying prevalence has been shown for pulmonary hypertension in different studies. Echocardiography, a noninvasive tool gives data about the presence of PH (increased tricuspid regurgitation, jet velocity and right ventricular dilation) and about structural abnormalities(intra cardiac shunts)[28].

Hence it is warranted for all COPD patients to have cardiac assessment at the time of diagnosis and/or during stable nature of the disease especially after an exacerbation.

AIM OF OUR STUDY

Primary Aim:

To evaluate the clinico-physiological characteristics of COPD and correlate them with the echocardiographic findings.

Secondary Aim:

To identify the predictors of pulmonary hypertension in COPD patients.

MATERIALS AND METHODS:

Source of data:

Patients diagnosed as COPD based on spirometry in the department of Respiratory medicine, PSG Hospitals affiliated to PSG IMSR located at Coimbatore, Tamil Nadu, India.

Sample Size:

Forty Subjects.

Study Duration:

May' 2013 to May' 2014.

Study Design:

Prospective cross sectional

INCLUSION CRITERIA:

- Age of onset of disease >40 years.
- Patients with symptoms suggestive of copd.
- Diagnosis of copd based on GOLD criteria.
- Willing to participate in the study

EXCLUSION CRITERIA:

- History suggestive of asthma.
- Other lung diseases that significantly contribute to decline in lung function.
- Patients with clinically evident active pulmonary tuberculosis.
- Patients with primary cardiac disease.
- Patients who have poor echo window.
- Ongoing or recent exacerbation of copd within 2 weeks prior to the enrollment in the study.
- Coexisting conditions that are contraindications or render forced expiratory maneuver difficult to perform.

ANTHROPOMETRIC MEASUREMENTS:

Weight and height are measured according to WHO recommended procedure.

Measurement of weight:

The weight of the study subjects were measured using the conventional standard weighing scale(Digital SECA Weighing scale, Model 753 E). With light clothing and without any foot wear, subjects were asked to stand on the platform of the weighing scale with bodyweight evenly distributed between both feet and weight was measured to nearest 0.1 kg.

Measurement of Height:

The height was measured using the stadiometer. The subjects were asked to stand in erect position without foot wear. They were asked to put their feet together and stretch upwards to the fullest extent with the arms hanging on the side. The height was measured to nearest 1 cm.

EVALUATION PLAN:

Patients diagnosed as COPD were screened for inclusion/exclusion criteria. The eligible subjects were explained

about the study and those willing to participate were enrolled. After getting written consent, they were interviewed for socio demographic details, medical history and subjected for thorough clinical examination. Based on GOLD criteria are classified as mild, moderate, severe, very severe disease based on post bronchodilator spirometric FEV1 >80%, FEV1 <80% to >50%, FEV1 <50% to 30%, FEV1 <30% respectively(Table 2). Six Minute Walk Test was done according to American Thoracic Society(ATS) recommendations. Echocardiography was done according to the guidelines by American Society of Echocardiography followed by cardiologist opinion was obtained.

DATA ANALYSIS

Statistical analysis was carried out using SPSS version.17 software. For continuous variables, mean, standard deviation were calculated and independent 'T' test was used for comparison. Categorical variables were expressed in percentage and Chi –square test was used for comparison. Statistically significant variables were subjected to multiple logistic regression.

Table.2: GOLD classification of COPD based on airflow limitation

GRADE	POST BRONCHODILATOR FEV1 in COPD patients having FEV1/FVC less than 0.7
I- MILD COPD	**FEV 1 ≥ 80% of predicted**
II- MODERATE COPD	**50% ≤ FEV1 less than 80% of predicted**
III- SEVERE COPD	**30% ≤ FEV1 less than 50% of predicted**
IV- VERY SEVERE COPD	**FEV 1 less than 30% of predicted**

FLOW DIAGRAM OF STUDY DESIGN:

Patients who have been diagnosed as COPD by GOLD criteria will be screened for inclusion/exclusion criteria.

Eligible candidates are explained about the study. Written informed consent is obtained from all eligible subjects who are willing to participate in the study.

Enrolled subjects will be interviewed for sociodemographic details.

They will be subjected to thorough clinical examination.

Echocardiography will be done to the above patients and cardiologist opinion will be obtained.

All collected data by above methods will be appropriately entered in case record form and analysed.

REVIEW OF LITERATURE:

HISTORY OF COPD:

Charles Fletcher [16,17] in 1977 described COPD as two entities, the one with chronic airflow limitation and the other with mucus hypersecretion. Fletcher and Peto postulated that the decline in FEV1 in susceptible smokers is more compared to non smokers and few smokers. Smoking cessation in susceptible smokers will prevent the rapid decline in FEV1.

SANCHEZ-SALCEDO et al.[18] in their study with 103 younger and 463 older patients for 2 years found that (59%) of the younger patients were ‘‘active smokers’’ compared with only 20% of the older group. Those who continues to smoke had rapid decline in lung function.

The Framingham cohort showed less decline in women who continued to smoke compared with men (23.9 versus 38.2 mL per year), and fewer female smokers developed airflow obstruction (24.2%) than male smokers (33.0%)[19] .

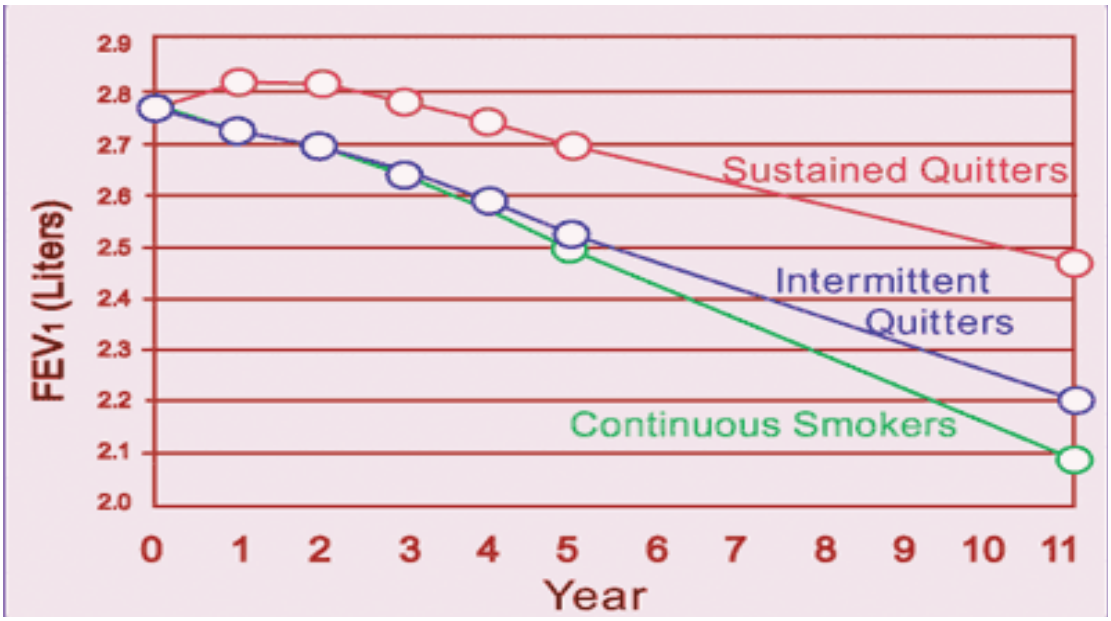
Emphysema is derived from Greek terminology which mean ‘ to blow into’, so “air-containing” or “inflated.” In 1679, Bonet described it as “voluminous lungs” and Morgagni in 1769 called it as turgid because of air.

The enlarged airspace in emphysema was described by Ruysh in 1721. Mathew Bailie in 1807 clearly recognized the destructive character of emphysema.

Laennec differentiated interstitial emphysema from emphysema proper and illustrated increased collateral ventilation, air trapping as features of emphysema. He showed the peripheral airways as the primary site of pathology in emphysema and enlarged airspaces can also occur with increasing age. Laennec described the association of emphysema with chronic bronchitis. In 1952, J. Gough showed the anatomy of pulmonary emphysema by paper mount technique. He illustrated centrilobular emphysema then distinguished it from panacinar emphysema. The microscopic illustration of emphysema was given by McLean. He demonstrated the relation of destructive alteration to inflammatory changes in bronchioles with changes in the vessels.

Ciba Guest Symposia (1959) denoted emphysema as “a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls”. Emphysema according to National Institutes of Health committee - “ when there was non uniformity in the pattern of respiratory airspace enlargement, and orderly appearance of the acinus and its components are disturbed”. The emphysema was considered as a part of airspace enlargement. The term was applicable to air space dilatation beyond the terminal bronchioles, existing with /without fibrosis or destruction.

Figure. 2. Lung Health Study showing changes in spirometry. Intermittent quitters (——) , continuous smokers(——) and sustained quitters



COPD phenotypes were described based on natural history and response to therapy[20]. They are

1. The frequent exacerbator;
2. The overlapping COPD/asthma patient
3. The emphysema-hyperinflation patient.

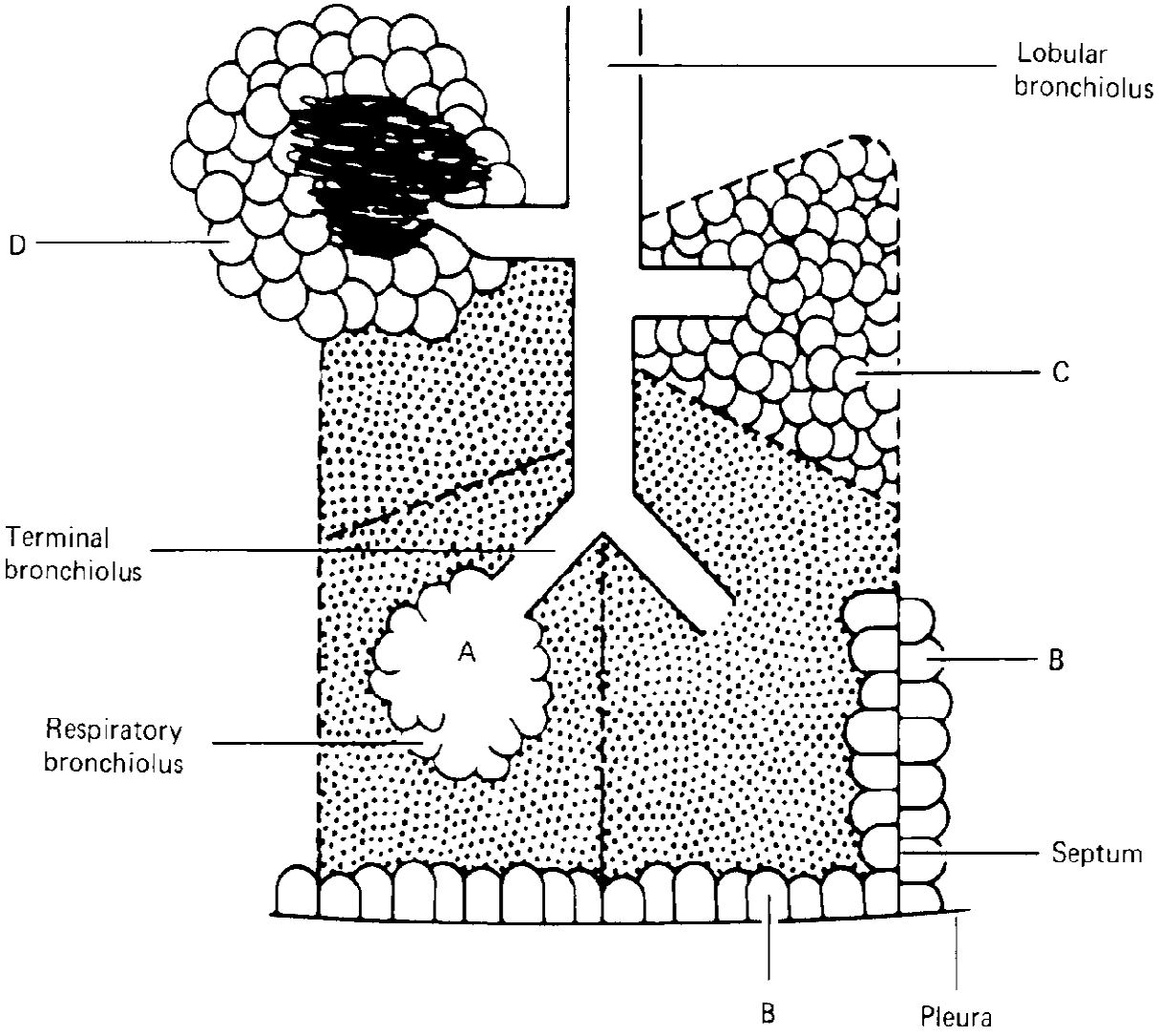
Recently due to increased use of HRCT Thorax in evaluating patients has led to description of two more phenotypes of COPD.

1. COPD with bronchiectasis
2. CPFE- Combined pulmonary fibrosis and emphysema[21] .

Chronic obstructive pulmonary disease (COPD) causes pathological change in four various lung compartments - central and peripheral airways, parenchyma , pulmonary vasculature, varying among individuals. Bullae is as an emphysematous space more than 1 cm in diameter. The classification of emphysema is based on the involvement of acini. The four recognized patterns are centriacinar, panacinar, paraseptal and irregular emphysema. In panacinar emphysema, the acinus will be almost uniformly involved; When the proximal portion of acinus is predominantly affected then it is called as proximal acinar emphysema(centrilobular emphysema). The destruction of the distal part (alveolar sacs and ducts) with relative sparing of the proximal portion, then it is distal acinar emphysema or paraseptal emphysema .The irregular involvement of acinus is termed asirregular emphysema or paracicatricial emphysema.(Figure 3).The centriacinar and panlobular emphysema were common compared to other types.

The physiological alterations in COPD are increased mucus secretion, ciliary impairment, airflow obstruction and hyperinflation , altered exchange of gases, pulmonary hypertension, systemic effects.

Figure. 3. Anatomic changes of emphysema. *A*. Centriacinar . *B* . Distal acinar. *C* .Panacinar . *D*. Irregular (scar). Image courtesy- Fishman's pulmonary diseases and disorders.

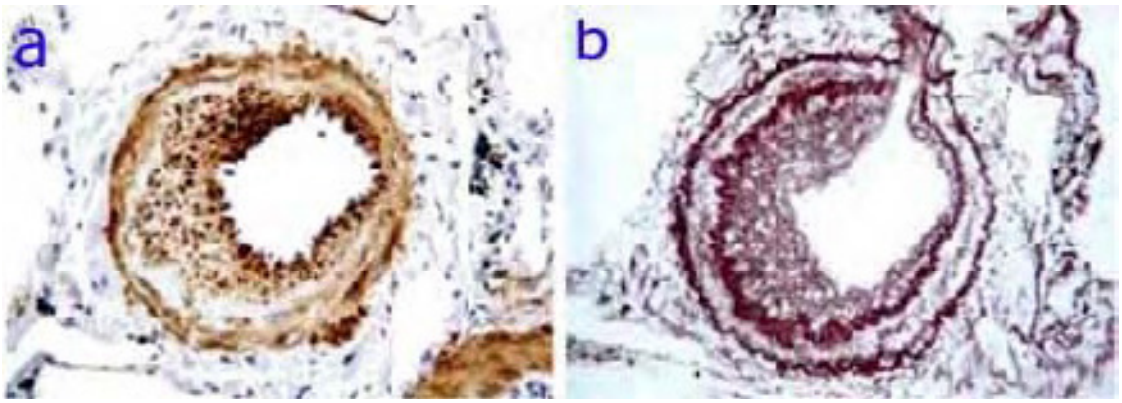


.Pulmonary vasculature

The changes in pulmonary vasculature begins early during the course of the disease [22].The wall of the vessel thickens and therefore endothelial dysfunction occurs[23]. Smooth muscle of the vessel enlarge followed by infiltration in the wall of blood vessels [24]. During advanced stages of COPD,

deposition of collagen along with emphysematous destruction of the capillary bed lead to pulmonary hypertension [25].

Figure 4 .Pulmonary muscular artery of a COPD patient – Thickened intima with narrowed lumen



a) Immunostaining - more intimal smooth muscle cells.

b) Orcein stain - Increased elastic fibre deposits in intima

Pulmonary Hypertension:

Pulmonary hypertension is defined as an increase of the mean Pulmonary artery pressure >25 mmHg at rest measured during right heart Catheterization [26]. To define Pulmonary Arterial hypertension(PAH) the patient should also have documented pulmonary wedge capillary pressure less than 15 mmHg.

Diagnosis of PHT:

PH is often a multifactorial disease. The diagnosis of PH should be stepwise, to confirm the existence of the disease and to identify the cause.(Figure 5)

Table 3. Clinical classification of pulmonary hypertension

1 . PAH

a. Idiopathic PAH

b. Heritable PAH(BMPR2)

2. PH secondary to left heart disease

3. PH secondary to lung disease and/or hypoxia

a. Chronic obstructive pulmonary disease

b. Interstitial lung disease

c. Sleep disordered breathing

d. Developmental lung diseases

e. Other pulmonary diseases with mixed restrictive and obstructive pattern

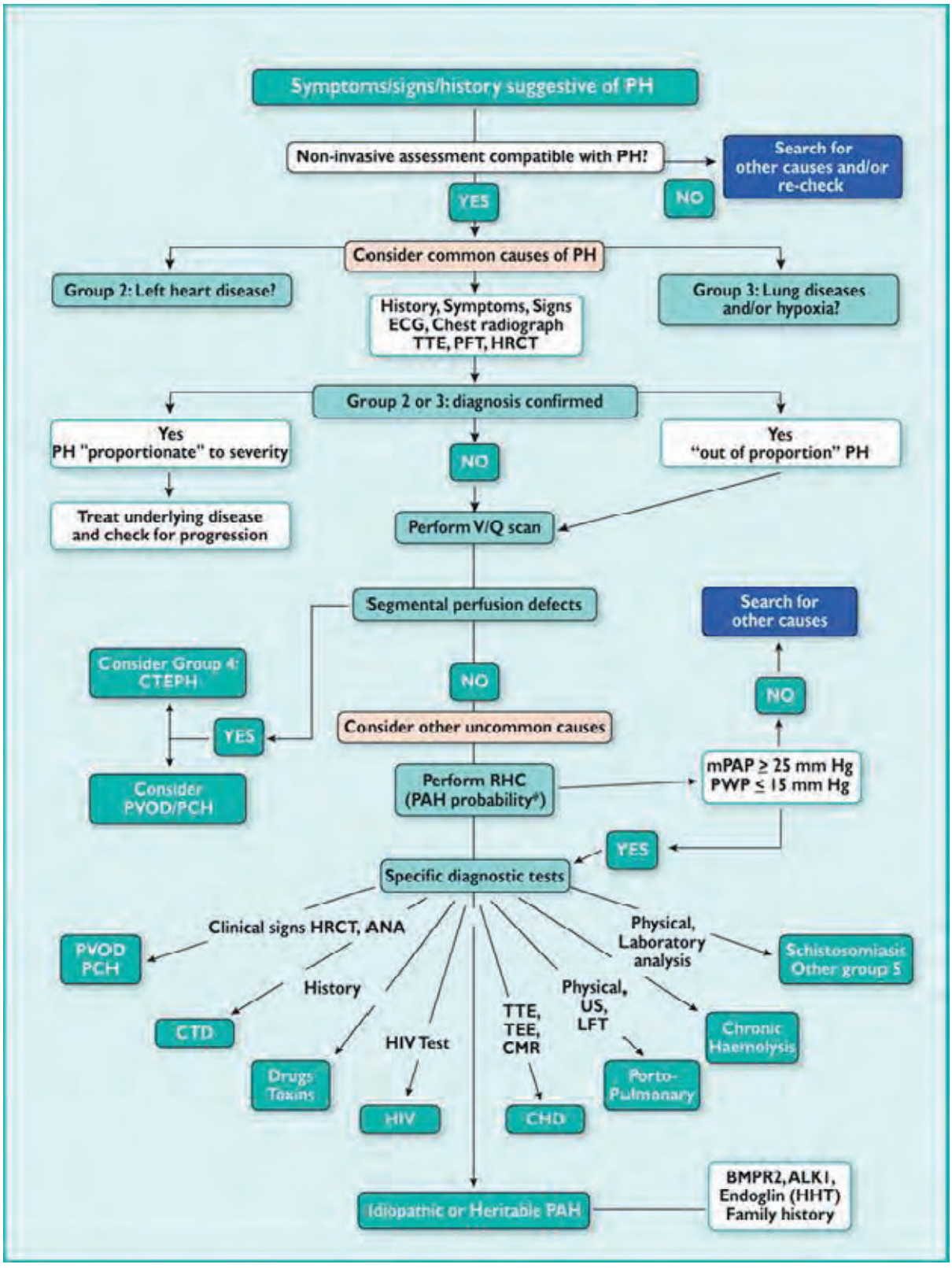
f. Alveolar hypoventilation disorder

g. Chronic exposure to high altitude

4. CTEPH

5. PH with unclear multifactorial mechanisms

Figure 5. Approach to a patient with Pulmonary hypertension



ECG:

Classical changes are hypertrophy and strain of right ventricle. Hypertrophied right ventricle and deviation towards right axis are found in 87% and 79% of patients respectively [27]

Right heart catheterization:

It helps to confirm the severity of the PH, check for vasoreactivity and to perform pulmonary angiography. The variables recorded are cardiac output, right atrial and ventricular pressure, PAP and pulmonary artery occlusion pressure (wedge pressure)[29]. Vasoreactivity test helps to identify candidates who will be benefited by calcium channel blockers. The test is said to be positive when mean PAP is less than 40 mmHg with a rise or no change in output.

Echocardiography:

Echocardiography, a noninvasive tool gives data about the presence of PH (increased tricuspid regurgitation, jet velocity and right ventricular dilation) and about structural abnormalities(intra cardiac shunts)[28]

Estimate of Pulmonary artery pressure:

Systolic pulmonary artery pressure (sPAP) is assumed equal to right ventricular systolic pressure(RVSP) in the absence of stenosis in pulmonary valve or outflow tract obstruction. RV systolic pressure can be determined by addition of right atrial (RA) pressure (RAP) to the pressure gradient between the

right chambers . The pressure gradient between the right chambers can be calculated using the modified Bernoulli equation:

$\Delta P = 4 \times v2$; v is the tricuspid regurgitant velocity (TRv) [33,34,35,36].

McQuillan BM et al [37] illustrated that TRv > 2.8 m/s is a reasonable cutoff to define elevated pulmonary pressures corresponding to a right atrioventricular pressure gradient > 31 mm Hg(figure 7), except in elderly and obese patients. Tramarin R et al, showed the ability to determine tricuspid jet in COPD patients is lower than in non COPD group with a range from 24% to 77% [38,39,40]

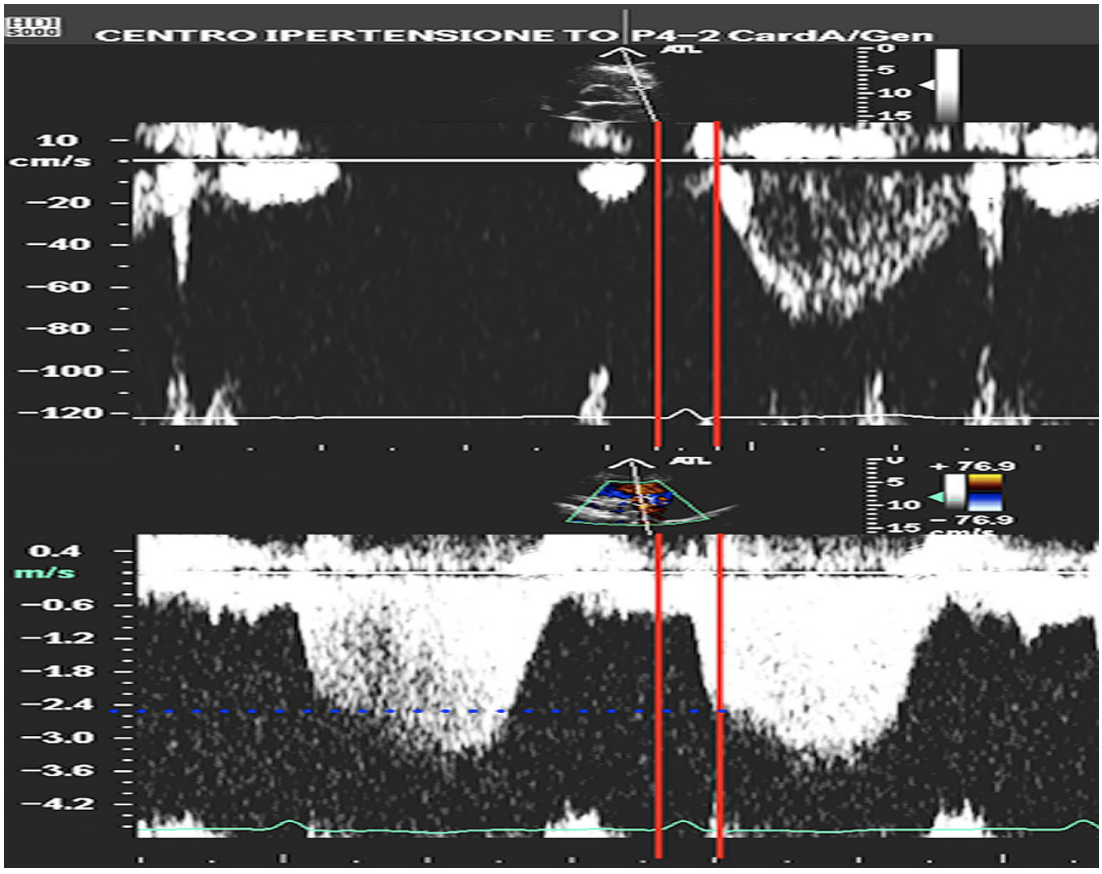


Figure 6. Assessment of right ventricle during opening of pulmonary valve. Transpulmonary flow (top) and Regurgitation in tricuspid valve (bottom).

The major concern during evaluation of sPAP by echocardiography is the risk of underestimation of sPAP. This is probably due to the frequent underestimation of RAP and TRv. False negative results can be minimized by measuring TRv in multiple views, by using color flow Doppler with or without contrast[41,42].

Kircher BJ et al [43] demonstrated the non invasive estimation of RAP by measuring the size of inferior venacava during respiration. For visualising IVC, the patient should be in supine position and in the subcostal view . The diameter should be measured at end-expiration and at end-inspiration within 2 cm of the right atrium

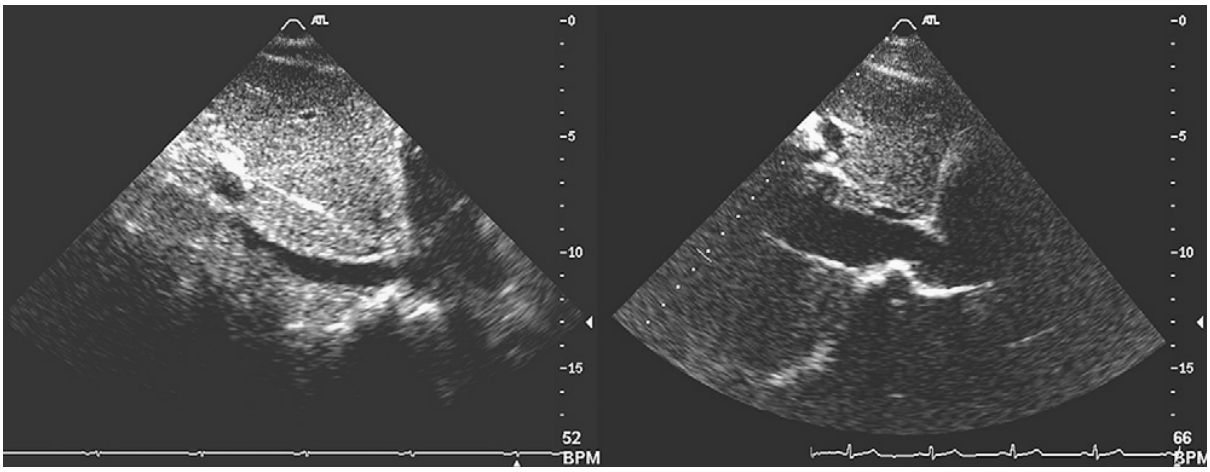


Figure 7 .IVC visualized in the subcostal view.

Left – IVC normal diameter. Right – IVC dilated

Pulmonary hypertension in COPD:

Elwing J et al [30] in their study of Pulmonary hypertension in COPD patients showed 10%-30% of patients with moderate to severe obstruction have elevated pulmonary pressures. Majority of PH in COPD is of mild to moderate

type and severe PH occurs in less than 5% of patients. Oswald-Mammosser M et al [31] showed that COPD associated with PH have both increased mortality and morbidity with a 5-year survival of 20% to 36 even in the era of long-term oxygen therapy. A cohort study of COPD patients by Thabut G et al [32] who had undergone Lung volume reduction surgery, 50% had mean PA pressure above 25 mm Hg. (**Figure 8**).

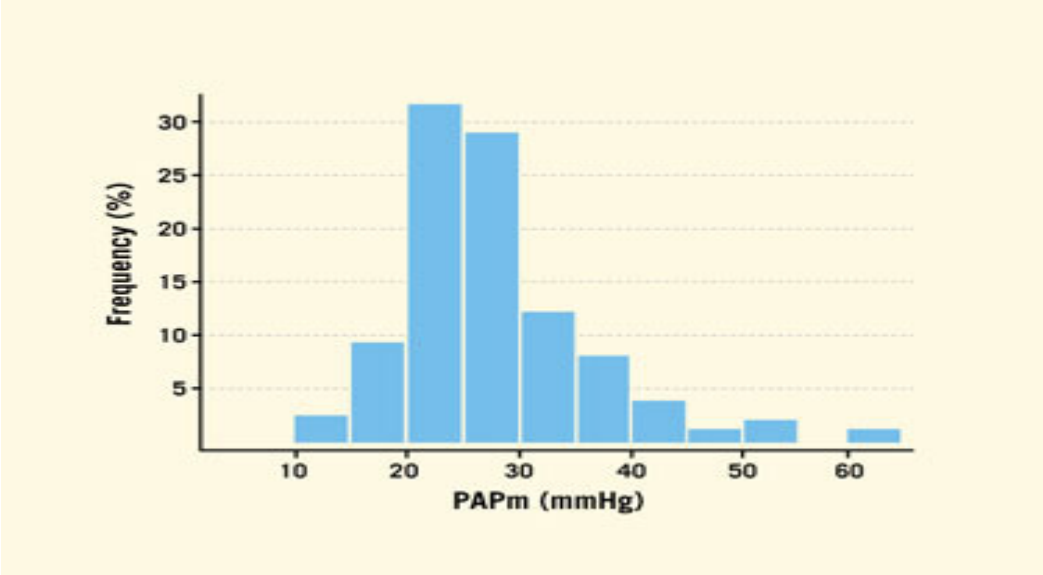


Figure 8 . Distribution of Pulmonary artery pressure

N.K.GUPTA et al evaluated 40 COPD patients with echocardiography and found high prevalance of PH, cor pulmonale, left ventricular dysfunction among more severe COPD [44]. M.A.HIGHAM et al[45] analysed the utility of echocardiography in assessment of pulmonary hypertension secondary to COPD at imperial college school of medicine,

london among 70 COPD patients and showed significant correlation of TTPG(transtricuspid pressure gradient) with FEV1 of r=-0.26,p=0.05. B SHRESTHA et al did echo for 507 COPD patients who attended nepal medical college teaching hospital , Attarkhel and showed that 49.1% had mild PAH and 56.3% had features of corpulmonale [46].

ANDREW C. STONE et al [47] subjected 43 COPD patients for echo. 23 patients had PAH(RVSP >45mmHg), of which 16 died during 1-year follow up compared with 5 of 20 patients with no PAH. They showed that presence of pulmonary hypertension is correlated with increased mortality in patients admitted with COPD. Sultan et al[57] found Tricuspid regurgitation jet in 70.9% of patients diagnosed with COPD. Increased pulmonary artery systolic pressure was noted in 51% of patients with TR (36% of total patients)

Burgess et al noted TR in 68% of patients with COPD[61].Gupta et al[44] found TR in 67.5% of study population and significant pulmonary hypertension was shown to be present in 63%.

Chatila et al found a 30% prevalence of pulmonary hypertension among the stable COPD[63]. Similarly 30 % and 40% prevalence of pulmonary hypertension was reported by Falk et al and Chaouat et al respectively[64,65].

Matsuyama et al[66] have found elevated pulmonary artery systolic pressure in 32.8% of patients with COPD. Weitzenblum et al found pulmonary hypertension in 35% of patients with COPD measured invasively[67]. Burgess et

al[68] have found elevated pulmonary systolic pressure in 34.4% of COPD patients.

A recent small cohort reported that the frequencies of PH in mild, moderate, severe, and very severe COPD were 16.67 %, 54.55 %, 60.00 %, and 83.33 %, respectively[44]. In another study, the frequency of PH was also found to be 25 %, 43 %, and 68 % in mild, moderate, and severe COPD, respectively[62] . Fayngersh V et al studied the prevalence of PH in 105 stable COPD patient and found 60% (n=63) of patients with pulmonary hypertension. In their study, there was a significant association between FEV1 and pulmonary hypertension. COPD patients with PH had lower FEV1% predicted than the patients without pulmonary hypertension(51.8 ± 18.8 vs. 62.7 ± 20.5%, P = 0.006)[69]

In 2002, Scharf et al[70] studied the hemodynamic characterization in patients with emphysema. They showed that COPD patients with pulmonary hypertension had lower FEV1 compared to those without FEV1 which was statistically significant. Mammosser et al[31] in their study on COPD patients to assess pulmonary hypertension enlightened that subjects with pulmonary hypertension had lower FEV1 than those without pulmonary hypertension. Bishop et al[71] used different non invasive techniques in predicting pulmonary artery pressure including echocardiography and found no correlation between severity of COPD and pulmonary hypertension.

Left Ventricular Diastolic Dysfunction(LVDD) in COPD:

Abroug F et al [48] in their study found 32% of patients with LVDD during COPD exacerbation. Caram et al from their study with 25 mild/moderate COPD and 25 severe/very severe COPD patient found mild left diastolic dysfunction among 88% of patients irrespective of COPD severity [49].Boussuges et al. found a prevalence of 76% vs. 35% of LVDD in COPD patients compared to controls [50]. Rutten et al. and Funk et al. reported a prevalence of 50% LVDD in their study [51,52]. Freixa et al. found a lower frequency of LVDD (12%) in COPD patients [53.] Schoos et al found LVDD in 66% of COPD patients . They showed that LVDD was not significantly associated with exercise capacity ($P = 0.278$) [73]. Left diastolic dysfunction can be asymptomatic or manifest with classical heart failure symptoms. Diastolic heart failure is common in older age group, Hypertension , Diabetes Mellitus, cardiac ischemia and obesity 5. Fayngersh et al[69] evaluated the etiology and distribution of pulmonary hypertension in stable COPD subjects by retrospective analysis. In the above study, 105 had adequate tricuspid regurgitant jet for measuring pulmonary pressure. They had a cut off of 36 mmHg for defining pulmonary hypertension. They noted a prevalence of 60% (ie sixty patients out of 105 had pulmonary hypertension with a mean value of 45 ± 6 mmHg. Patients with pulmonary hypertension had higher age (71.1 ± 11.8) when compared to those without increased pulmonary pressure

with a mean of 63.7 ± 10.2 year, which was statistically significant ,'P ' value of 0.001. Patients with pulmonary hypertension had decreased predicted percentage forced expiratory volume in first second with 51.8 ± 18.8 as mean value than those without elevated pressure with P value of 0.006). By Multivariate logistic regression these two variables withstood their significance. Lung function variables like residual volume and total lung capacity , demographic variables like BMI, gender, pack years and smoking status did not correlate with pulmonary hypertension.

Gologanu et al[100] noticed a worse outcome for patients with pulmonary hypertension. They also had an increased frequency of exacerbation, an increase in the healthcare cost and a poor quality of life. Vasoconstriction of capillaries secondary to hypoxia, dysfunction of endothelium were the proposed mechanism. Unexplained hypoxemia and breathlessness which is not correlating with the decline in pulmonary function, the possibility of pulmonary hypertension should be considered. The development of PH during exercise is an independent predictor for the development of pulmonary hypertension at rest . The cardiac consequences of pulmonary hypertension on the right ventricle can br screened early by echocardiography. Systolic pressure of pulmonary artery has high negative predictive value, hence it helps to rule out significant pulmonary hypertension , avoiding invasive catherisation. Catheterization of right heart is not readily available in all centres.

Ertan C et al[101] analysed by echo the distensibility of pulmonary artery in patients with COPD. This was a prospective study comparing male patients having COPD with healthy controls. Fractional shortening of right pulmonary artery, stiffness of pulmonary vessels were studied. The study sample was 54 COPD patients and the control group had 24 volunteers. The normal individuals had good pulmonary artery distensibility compared to patients with COPD. COPD had a mean of 13.3 ± 8.1while healthy population had a mean of 27.6 ± 4.9 with 'P' value of less than 0.001. TAPSE had positive association with distensibility of pulmonary artery. The distensibility had inverse correlation with pressure in pulmonary artery. COPD patients had impaired stiffness of pulmonary vessels and had inverse association with disstensibility. Significant correlation noted between mean PAP and isovolumic acceleration of right ventricle.Thickness of right ventricular wall ($p < 0.01$). Impaired right ventricle and more thickened right ventricular wall were found with mean PAP (18 ± 3 mm Hg) in non PH group.

Hoffmann et al[102] studied whether remodeling of pulmonary vessels in pulmonary hypertension of COPD and idiopathic pulmonary fibrosis had similar biomarkers. They combined entire genomic microarrays with profile of pulmonary artery microdissected by laser capturing. Interaction of receptors at extracellular level and the retinol pathway were the predominant mechanism involved. Immunohistochemical staining and polymerase chain reaction found

type 3 collagen, von Willebrand factor , thrombospondin 2 were altered among the extracellular matrix pathway. Many genes are linked in the metabolism of retinol and extracellular matrix path, enabling discrimination of vascular changes in idiopathic pulmonary fibrosis and COPD.

Gokdeniz T et al[103] evaluated by means of two dimensional speckle tracking echocardiography among 135 COPD and 37 observation arm, the relation between BODE index and function of right ventricle. Compared to observational arm, patients with airflow obstruction had diastolic dysfunction. Functional parameters of right ventricle like TAPSE, strain of free wall fractional change in area of right ventricle, TEI index had significant correlation with BODE index. Multivariate analysis showed strain of free wall as the significant variable.

SIX MINUTE WALK DISTANCE:

In 1960, Balke inorder to evaluate the functional capacity developed a simple test, during which the distance walked in a defined time period was measured[95]. Cooper et al for evaluating the physical fitness of healthy individuals developed a 12 minute field performance test [96]. Mcgavin et al used walking test to assess disability in patients with chronic bronchitis[97]. Butland found walking 12 minutes was too exhausting for patients with respiratory disease, both six and twelve minute walk test performed equally[98]. Solway et al in their analysis on functional walking found that six minute walk test is reflective of daily activities, better tolerated and easy to administer than the other walk tests[99].

The test does not require sophisticated equipments. Walking is a daily performed activity. The distance covered over a period of six minutes are measured. The integrated response of the cardiovascular, pulmonary and other systems are evaluated.

INDICATIONS :

1. To compare pre and post treatment response

   Lung resection

   Lung transplantation

   Lung volume reduction surgery

   Pulmonary rehabilitation

COPD

Pulmonary hypertension

Heart failure

2. To assess functional status (single measurement)

   COPD

   Cystic fibrosis

   Heart failure

   Peripheral vascular disease

   Fibromyalgia

   Older patients

3. Predictor of morbidity and mortality

   Heart failure

   COPD

   Primary pulmonary hypertension

CONTRAINDICATIONS:

Absolute contraindications :

1. Unstable angina during the previous month
2. Myocardial infarction during the previous month.

Relative contraindications:

1. Resting heart rate of more than 120,
2. Systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

TECHNICAL ASPECTS:

Location

Indoors are always preferred for 6MWT unless the outside weather is comfortable. The test is carried on a lengthy, flat and straight with enclosed corridor having a hard surface. The corridor should have 30 metres length and marked every 3 metres. The turning areas are marked with a traffic cone . The start line and the end line are highlighted on the floor by bright colored tape.

Patient preparation

Patients are advised to

1. Wear Comfortable clothing
2. Wear Appropriate shoes
3. Use the routine walking aids at the time of test (walker).
4. Continue routine medications
5. Take a light meal
6. Avoid vigorous exercise within 2 hours prior to test.

Factors influencing the test:

The test is negatively affected by

1. Shorter height
2. 2Older age
3. Higher body weight

4. Female sex
5. Impaired cognition
6. A shorter corridor with more turns
7. Musculoskeletal disorders (arthritis, lower limb injuries, muscle wasting.)

The test is positively influenced by

1. Taller height
2. Male sex
3. High motivation
4. Already performed
5. Medication for a disabling disease taken just before the test
6. Oxygen supplementation in patients with exercise-induced hypoxemia

SPIROMETRY

FEV1, FVC MANOEUVRE:

FVC is defined as the maximum amount of air exhaled with maximum effort after a maximal deep inspiration, i.e. vital capacity carried with a maximal forced expiratory effort and expressed in litres at BTPS -body temperature and ambient pressure saturated with water vapour .

FEV1 is the maximum amount of air exhaled during the first second of a forced expiratory manoeuvre after a full inspiration, expressed in litres at BTPS.

BTPS correction:

Spirometry values are reported at BTPS . For volume type spirometer, the temperature within the spirometer must be measured at every breath. The ambient temperature is documented with accuracy of ± 1°C. When the temperature at ambient air changes quickly (more than 3°C in less than 30 min), sequential temperature corrections are needed. Potential problem occur when the tests are performed at lower ambient temperature (17°C). The barometric pressure is used to calculate BTPS correction factor.

Requirement:

Spirometer with an accumulating volume for ≥15 seconds and with capacity of calculating volumes of ≥8 Litres at BTPS with an accurate reading of at least ±3% is recommended. The total airflow resistance at 14.0 L/s should

be less than 1.5 cmH2O/ L/s The total impedence is calculated with the tubes, valves and filter included between the subject and the spirometer.

Procedure:

FVC manoeuvre has three phase

1. Maximum inspiration

2. Blast of exhalation

3. Continued complete exhalation to the end of test (EOT).

Spirometer calibration is checked. The subject is explained about the maneuver and history of smoking, current illness and treatment details should be documented. Weight, height are measured. Test should be demonstrated to the subject including exact posture with slight elevated head , Position of the mouthpiece , rapid inhalation and complete exhalation with maximal force. The tests are repeated for a minimum of three manoeuvres and maximum of eight manoeuvres.

Criteria for starting the test:

The exact timing of the test during start is determined by back extrapolation method . For all timed measurements, the start is defined from back extrapolation by the new ‘‘time zero’’. Manual measurements can be done from the volume–time curve by tracing back the steepest slope by the extrapolation method. The largest slope averaging above 80 millisecond period

is recommended for computerized data. The EV should be less than 5% of the FVC or 0.150 Litre for achieving accurate time zero and to ensure that FEV1 is obtained from a maximal effort curve. An unnecessary prolonged effort can be avoided by terminating the test with an obvious hesitant start. The volume-time curve must have the expiratory flow tracing, complete prior inspiratory tracing and should include time zero (≥ 0.25 second, preferably ≥1 second prior to the beginning of exhalation).

Criteria to end the test:

Subjects are motivated to continue exhaling the air at the end of the test to get optimal effort . Reasonable FVC effort can be identified by EOT criteria.

The recommended EOT criteria are

1) If the subject has discomfort ,further exhalation should not be continued.
2) The volume–time curve showing no change in volume (less than 0.025 Litre for ≥1 second) and the subject had exhaled for ≥ 3 seconds and for ≥ 6 seconds, in children less than 10 yrs and adults more than10yrs respectively.

Acceptability criteria:

A. Within manoeuvre , if Spirogram is free from

1. Artefact

2. Cough during the first second of exhalation

3. Glottis closure that influences the measurement

4. Early termination or cut-off

5. Effort that is not maximal throughout

6. Leak

7. Obstructed mouthpiece

If Spirogram has

1. good start
2. Extrapolated volume < 5% of FVC or 0.15 L
3. satisfactory exhalation
4. duration of ≥6 s (3 s for children) or a plateau in the volume–time curve

B. Between manoeuvre :

1. The two largest values of FVC must be within 0.150 L of each other
2. The two largest values of FEV1 must be within 0.150 L of each other.

ECHOCARDIOGRAPHY:

In patients with Cardiopulmonary disease having significant clinical signs and symptoms , the right heart function plays an important role in morbidity and mortality. Right ventricle is not just a conduit of blood flow but also has prognostic significance in various clinical settings. It helps as a risk stratification factor, maintains low systemic venous pressure to prevent congestion of tissues or organs , affects left ventricular function by limiting LV preload in RV dysfunction due to ventricular interdependence. In patients with congestive heart failure and associated CAD, poor right ventricle ejection fraction has increased mortality. Inspite, the right ventricular assessment technique varies within clinicians and the methods , assessment proves to be fragile because the importance is stressed over the left sided heart assessments.

RIGHT HEART PARAMETERS :

Right ventricular (RV) size during systole and diastole

Right atrial (RA) size

RV systolic function

Fractional area change [FAC]

Tricuspid annular plane systolic excursion[TAPSE]

RV index of Myocardial performance [RIMP]

RV diastolic function

Right ventricular wall thickness

Systolic pulmonary artery pressure

Estimating right atrial pressure from inferior vena cava (IVC) size ,collapse

Pulmonary artery diastolic pressure(PADP)

IMAGING WINDOWS AND VIEWS:

The assessment of right ventricle systolic, diastolic function and right ventricle systolic pressure(RVSP) is made by the following views

Left parasternal longaxis (PLAX)

Subcostal view .

Apical 4-chamber

Modified apical 4-chamber

Parasternal short-axis (PSAX)

MEASUREMENT:

RV DIMENSION:

Right ventricle focused apical 4-chamber view is the best view to assess the right ventricular dimension. Crux and the apex should be focussed clearly to avoid foreshortening. RV enlargement is said to be present, when

Basal diameter > 42 mm

Midlevel diameter > 35 mm

The longitudinal dimension > 86 mm.

RA DIMENSION:

The apical four chamber view indicates the end diastole right atrial enlargement if RA area is more than 18 cm2,

RA length(major dimension) > 53 mm, and

RA diameter (minor dimension) > 44 mm .

Right ventricle outflow tract dimension:

The left parasternal short axis view is the best view to assess the distal diameter at the level of pulmonary valves. The proximal portion is also assessed to evaluate the right ventricle outflow tract. Diameter > 27mm at end-diastole at the pulmonary valve attachment indicates RVOT dilatation.

Right ventricle wall thickness:

RV wall thickness is measured from the subcostal view during diastole, using either two-dimensional imaging or M mode.

IVC DIMENSION:

IVC is best seen through the subcostal view. It also helps to measure IVC and assess collapse during inspiration. Diameter of inferior vena cava is measured proximal to the entrance of hepatic veins .Specific values rather than ranges of right atrial pressure must be used in the estimation of SPAP.IVC diameter less than 2.1 cm that collapses more than 50% during sniff indicates normal right atrial pressure of 3 mm Hg . IVC diameter more than 2.1 cm that

collapses less than 50% during sniff indicateshigh right atrial pressure of 15 mm Hg . Young athletes and patients on ventilator commonly have dilated IVC.

RV SYSTOLIC FUNCTION:

RV systolic function is assessed by parameters like TAPSE, RV FAC, RIMP, 2 D ejection fraction of RV, three dimensional ejection fraction of RV, longitudinal strain , Tricuspid lateral annular systolic velocity and strain rate. RV index of Myocardial performance :

RIMP is an index of overall right ventricle function. The estimate of RIMP more than 0.40 by pulsed Doppler and more than 0.55 by tissue Doppler suggest RV dysfunction.

TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION[TAPSE]:

TAPSE is a measure of longitudinal function of right ventricle. TAPSE less than 16 mm indicates systolic dysfunction of right ventricle. It is calculated from the tricuspid lateral annulus. It correlates with the values recorded by methods like radionuclide derived right ventricle ejection fraction.

FRACTIONAL AREA CHANGE [FAC]:

Two dimensional FAC in percentage gives an estimate of systolic function of right ventricle. Two dimensional FAC below 35% indicates right ventricle systolic dysfunction.

RV DIASTOLIC FUNCTION:

Right ventricle diastolic function can be assessed from tricuspid inflow by using pulsed doppler, from lateral tricuspid annulus , by imaging hepatic vein with doppler, and by measuring size and collapsibility of inferior vena cava. The parameters like deceleration time , E/A ratio, the E/E´ ratio are also used to measure the RV diastolic dysfunction.

GRADING OF DIASTOLIC DYSFUNCTION:

Impaired relaxation when tricuspid E/A ratio below 0.8

Pseudonormal filling when tricuspid E/A ratio of 0.8 to 2.1 and

Restrictive filling, if tricuspid E/A ratio more than 2.1

PULMONARY ARTERY SYSTOLIC PRESSURE:

With the assumption of no significant RVOT obstruction, TR velocity is made out which permits the estimation of RVSP.. The estimated right atrial pressure from size of inferior vena cava and its collapsibility is added . Tricuspid regurgitant velocity more than 2.8 to 2.9 m/s, corresponds to around 36 mmHg of systolic pulmonary artery pressure, assuming an RA pressure of 3 to 5mmHg, indicating raised pulmonary artery pressure. It varies with age , obesity status and should be correlated with the left heart findings.

PULMONARY ARTERY DIASTOLIC PRESSURE:

PADP is calculated from the end diastolic pulmonary regurgitant jet velocity by applying modified Bernoulli equation

PADP = 4 x (end diastolic velocity of pulmonary regurgitation)^2 + RA pressure.

The mean pulmonary artery pressure is estimated from the systolic and diastolic pressure by using the following formula

Mean Pulmonary artery pressure = 1/3(SPAP)+ 2/3(PADP).

It must be measured along with mean arterial pressure or systemic blood pressure. Invasive PVR measurement of less than 1.5Wood units (120 dynes . cm/s2) is normal. In clinical studies, significant pulmonary hypertension is defined as PVR of more than 3 Wood units (240 dynes . cm/s2).

Peak systolic velocity (PSV):

PSV < 11.5 cm/s identifies the presence of RV dysfunction with Sensitivity of 90%, specificity of 85%. It is less affected by HR, loading condition, and degree of TR

As echocardiography is the initial test used in the evaluation of symptomatic cardiovascular patients, the assessment of right heart structure and function along with left heart parameters proves mandatory.

RESULTS

We present our study results under the following description

1. Distribution of study variables
2. Comparison between physiologic variables
3. Correlation of variables between PH and non PH group

1. DISTRIBUTION OF STUDY VARIABLES:

Forty subjects were recruited in our study. All the participants were males (100%). The age of patients ranged from 40 to 80 years with a mean of 60.65 ± 9.42 years. Based on their current occupational status, 28(70%) subjects were currently employed and 12(30%) of study subjects were unemployed. Twenty five(62.5%) subjects were urban dwellers while 15(37.5%) subjects resided in rural area. All the forty of our study subjects consumed mixed diet. (Table 4).

. Dyspnoea severity was enquired according to MMRC scale. Sixteen(40%) of subjects had grade 1 dyspnoea, while grade 2 and grade 3 dyspnoea were reported by 20(50 %) and 4(10%) subjects respectively. None of them had grade 4 dyspnoea. In the previous year, 25(62.5%) subjects had atleast one exacerbation of their disease (Table 5).

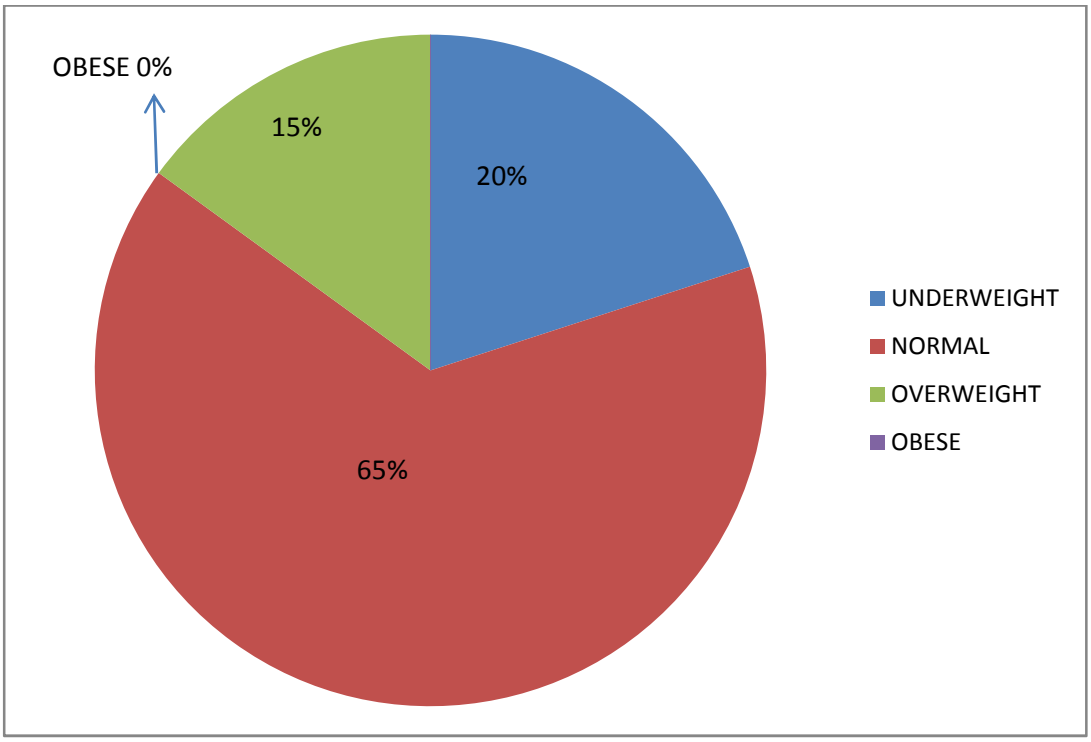
Table.4: Socio demographic characteristics of the study population

S.No	Variable	Sample(n = 40) subjects
1.	Age (in years)	60.65±9.42
2.	Male gender (%)	40(100%)
3.	BMI (in Kg/m^2)	21.44±3.49
4.	Socioeconomic status	
	Class 1	5(12.5 %)
	Class 2	22(55%)
	Class 3	9(22.5%)
	Class 4	3(7.5%)
	Class 5	1(2.5%)
5.	Diet	
	Vegetarian	0
	Mixed	40(100%)
6.	Dwelling	
	Urban	25(62.5%)
	Rural	15(37.5%)
7.	Current occupation status	
	Employed	28(70%)
	Unemployed	12(30%)

BODY MASS INDEX:

The mean BMI of the study group was 21.44 ± 3.49 Kg/m^2. Twenty six(65%) subjects had normal BMI. Underweight was present in 8(20%) of subjects. Overweight was documented in 7(17.5%) of subjects. None of our study population belonged to obese category.

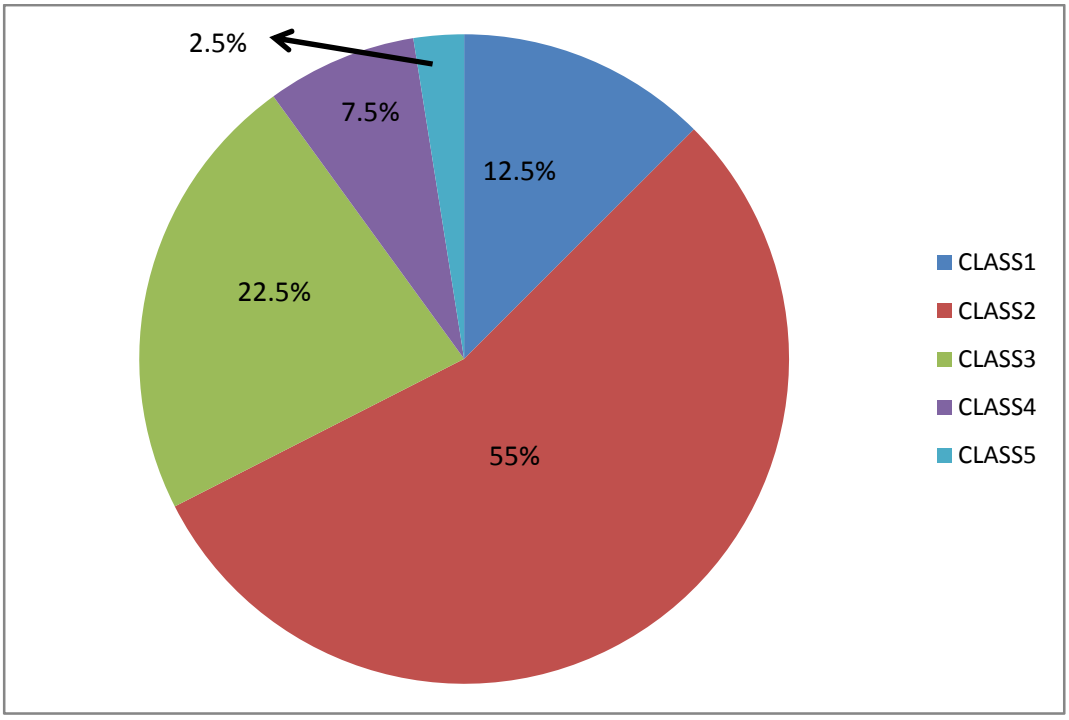
Figure 9. Distribution of BMI.



SOCIOECONOMIC STATUS:

Socioeconomic status was assigned according to All India Consumer Price Index (AICPI) for industrial workers –May 2013 . Twenty two(55%) of our study subjects were in class 2. Nine(22.5%) subjects were in socioeconomic class 3. Five(12.5 %) subjects were in class 1, 3(7.5%) subjects in class 4 and only one subject in class 5.

Figure 10 : Socio economic status of the study population



SMOKING PATTERN:

The mean smoking pack years of the study population was 43.47 ± 24.16 pack years and 35(87.5%) subjects in our study had more than 20 pack years while 15(12.5%) subjects had less than 20 pack years (Table 2).

DURATION OF DISEASE:

The mean duration of symptoms among our study subjects was 5.8 ± 3.5 years. Eighteen(45%) of them had symptoms more than 5 years and 22(55%) subjects had disease less than 5 years.(Table 2).

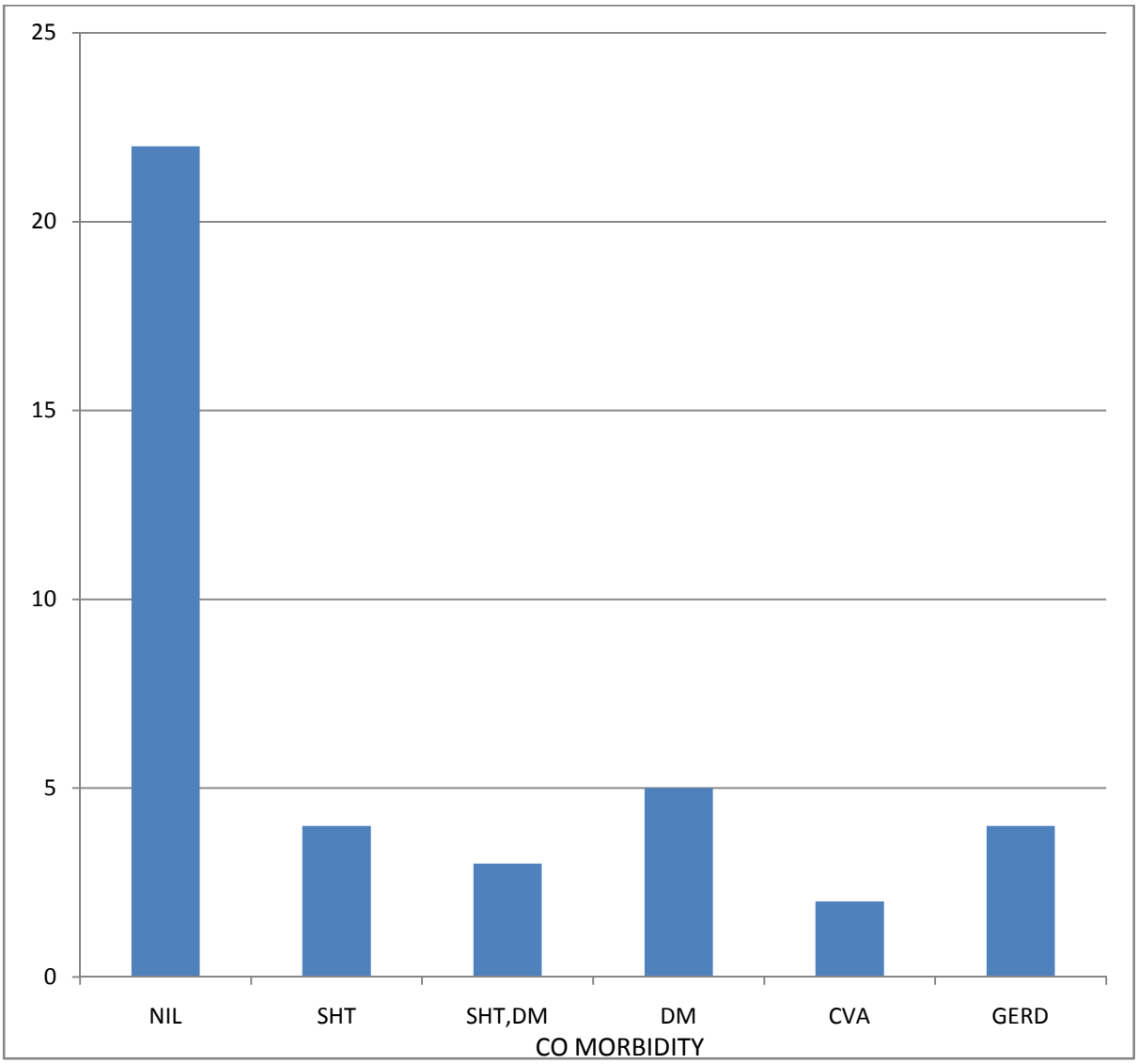
Table. 5 Disease specific characteristics of study population

S.No	Variables	Total subjects(n=40)
1.	Smoking pack years	
	More than 20 pack years	35(87.5%)
	Less than 20 pack years	5(12.5%)
2.	Duration of disease (in years)	5.8 ± 3.5
3.	Post bronchodilator FEV1 (in litres)	1.24 ± 0.49
4.	Post bronchodilator FVC (in litres)	2.25 ± 0.66
5.	Predicted FEV1 (in percent)	51.05 ± 16.09
6.	Spo2 (in percent)	97.25 ± 1.35
7.	6MWD (in metres)	492 ± 90
8.	Dyspnoea –MMRC grade	
	Grade 1	16(40%)
	Grade 2	20(50%)
	Grade 3	4(10%)
	Grade 4	0
9.	Co-morbidities	
	No comorbidity	22(55%)
	Systemic hypertension	4(10%)
	Type 2 Diabetes	5(12.5%)
	GERD	4(10%)

COMORBIDITIES:

Comorbidities were present in 18(45%) of subjects. Among the comorbidities, diabetes 5(12.5%) , hypertension 4(10%), Gastro Esophageal Reflux disease(GERD) 4(10%) were the commonest. In addition, both diabetes and hypertension were present in 3(7.5%) subjects. The other comorbidity noted in our study was Cerebro Vascular accident(CVA) in 4(10%) subjects.

Figure 11. Distribution of co morbidities



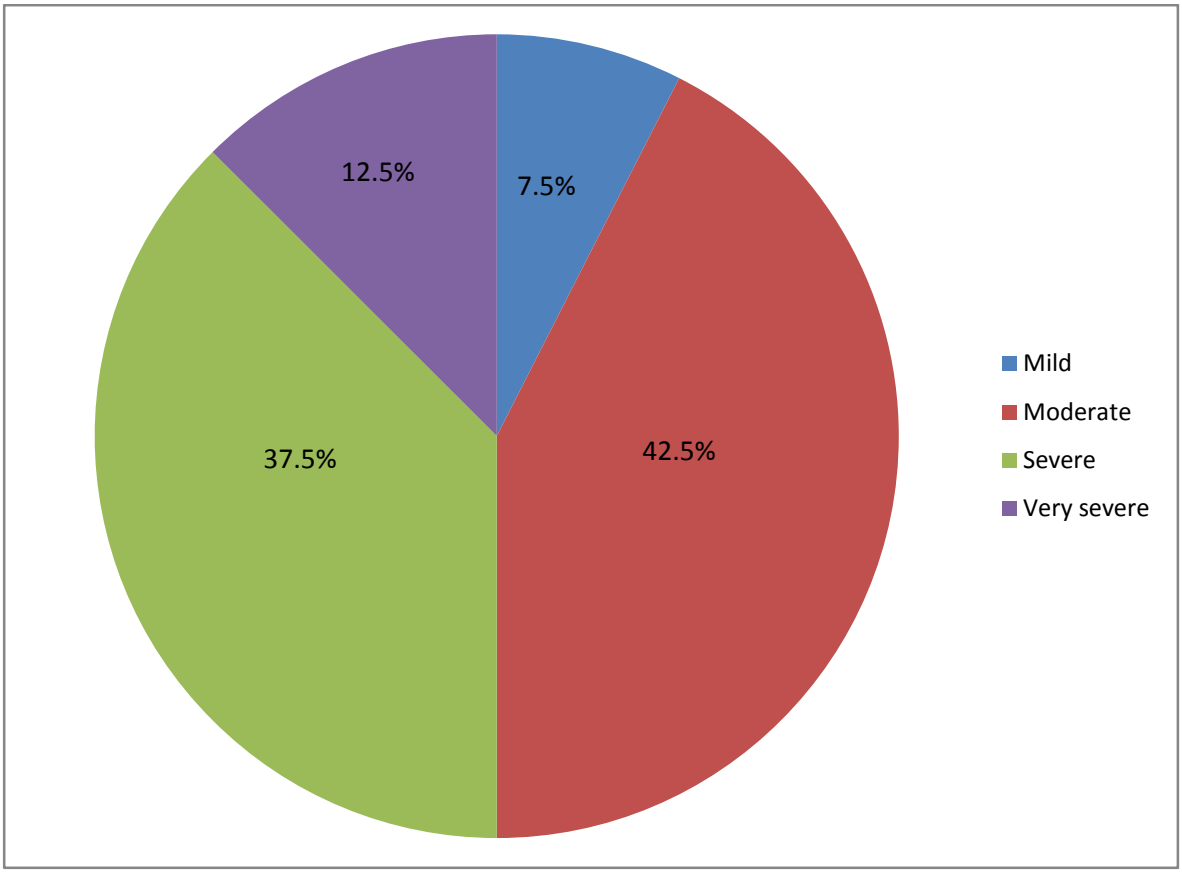
GRADING OF COPD BASED ON GOLD GUIDELINES :

The mean FEV1 among the COPD patients was 1.24 ± 0.49 litres , the mean FEV1 % predicted was 51.05 ± 16.09 % and the mean FVC was 2.25 ± 0.66 litres. Three (7.5%) subjects had mild disease, Moderate obstruction was present in 17(42.5%) subjects, severe obstruction was noted in 15(37.5%) subjects, very severe COPD was diagnosed in 5 (12.5%) subjects . In our study 32(80%) subjects had moderate to severe COPD (Table.3), (Figure.4).

Table 6. Distribution of the severity of COPD as per GOLD guidelines.

GOLD grading of severity of COPD	No of patients	Percentage
Mild	3	7.5%
Moderate	17	42.5%
Severe	15	37.5%
Very severe	5	12.5%

Figure 12. Distribution of the severity of COPD as per GOLD guidelines.



2. COMPARISON BETWEEN PHYSIOLOGIC VARIABLES

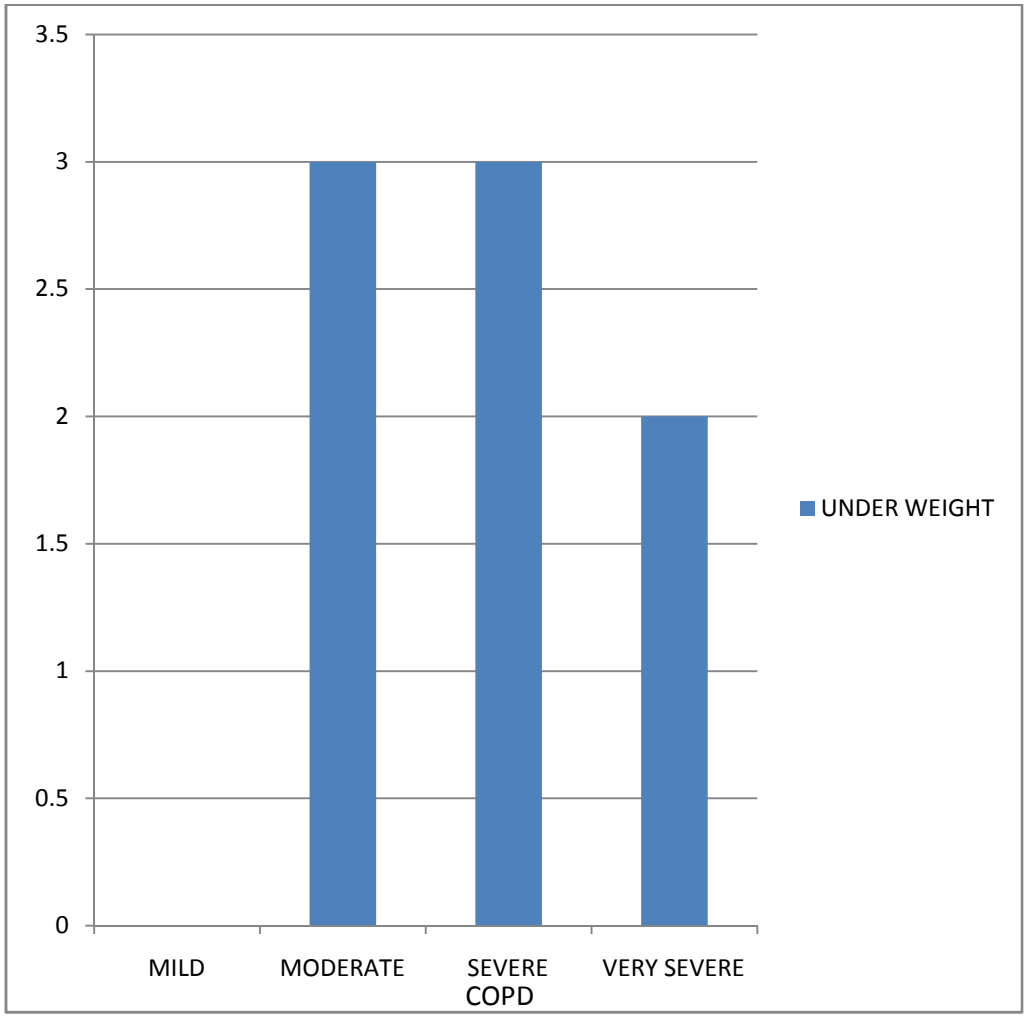
COMPARISON OF SEVERITY OF AIRWAY OBSTRUCTION WITH BMI.

When severity of COPD were compared with BMI, underweight was found in 3 patients of moderate COPD, 2 patients of severe COPD and 1 patient of very severe COPD. No underweight was found in mild COPD. Table 7 and Figure 5.

Table 7. Comparison of severity of airway obstruction with BMI.

Severity of COPD	Underweight	Normal	Over weight
Mild	0	3	0
Moderate	3	9	5
Severe	3	10	2
Very severe	2	3	0

Figure 13. Comparison of severity of airway obstruction with BMI.



COMPARISON OF SEVERITY OF COPD WITH DYSPNOEA GRADE:

Severity of dyspnoea was done by MMRC grading. Grade 3 dyspnoea was found in 50 % of very severe COPD patients. 18.8% of mild COPD, 56.2% OF moderate COPD and 25% of severe COPD had grade 1 dyspnoea. Severity of dyspnoea showed significant correlation with severity of obstruction with P value of 0.023.

Table 8 .Comparison between Severity of COPD and Dyspnoea grade

MMRC	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD
Grade 1	18.8%	56.2 %	25%	0
Grade 2	0 %	40%	45%	15%
Grade 3	0%	0%	50%	50%

('P' value = 0.023)

SIX MINUTE WALK DISTANCE:

The mean distance covered during six minute walk test was 492 ± 90 meters. Thirty seven(87%) subjects covered more than 350 meters. Only 3(13%) subjects walked less than 350 meters and they had very severe COPD ('P' Value = 0.001).

Table 9. Comparing severity of obstruction with 6MWD.

Severity of COPD	6MWD < 350 meters	6MWD > 350 meters
Mild	0	3
Moderate	0	17
Severe	0	15
Very severe	3	2
		P =0.001

Only 2(14%)vsubjects with pulmonary hypertension covered less than 350 meters, where as 12(86%) subjects with PH walked more than 350meters.

Table 10. Comparing six minute walk distance with pulmonary hypertension

Distance covered in 6MWD	Pulmonary hypertension (n = 14)
Less than 350 meters	2(14%)
More than 350 meters	12(86%)
	P = 0.232

PULMONARY HYPERTENSION:

The range of pulmonary artery pressure was from 15mmHg to 49mmHg. None of the patients had Systolic pulmonary artery pressure (s PAP) more than 50 mmHg. Pulmonary hypertension(PH) was found in 14(35%) of subjects. Among patients with PH, 4(28%) subjects had COPD symptoms for more than 5 years. Measurable tricuspid regurgitation(TR) was found in 20(50%) of our study subjects. Among those with measurable TR, pulmonary hypertension defined by systolic pulmonary artery pressure was documented in 14(70%) subjects.

Table 11. Frequency of pulmonary hypertension among COPD.

Pulmonary hypertension	No of subjects n = 40	Percentage
Present	14	35%
Absent	26	65%

The distribution of pulmonary hypertension among mild, moderate, severe and very severe COPD were 33.3%, 26.7%, 35.3% and 60% respectively('P'= 0.607).

Table 12 . Distribution of Pulmonary hypertension among study subjects.

COPD severity	No of patients with PH	Percentage with PH
Mild	1	33.3%
Moderate	4	26.7%
Severe	6	35.3%
Very severe	3	60%

Figure 14 . Distribution of Pulmonary hypertension among study subjects.

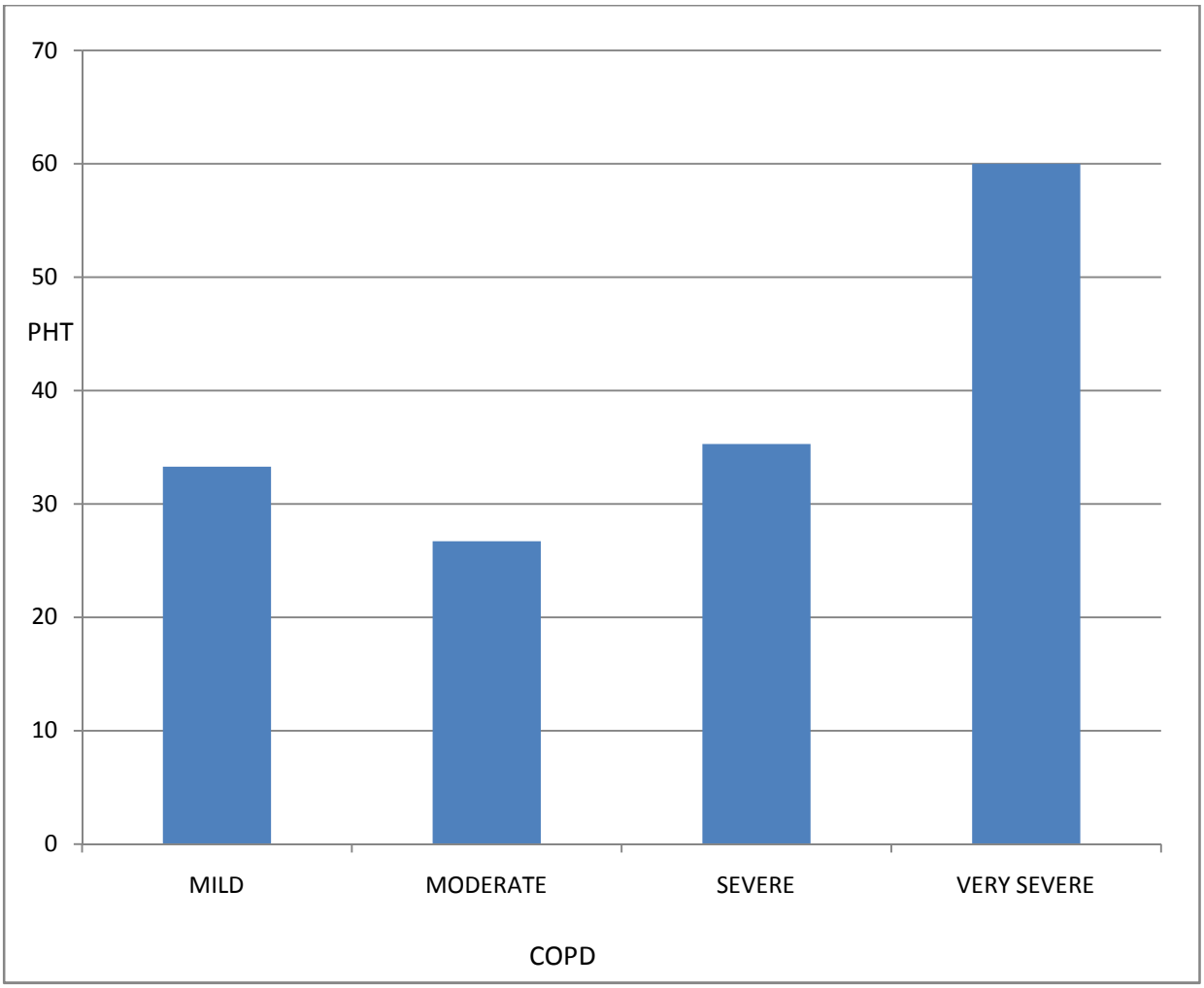


Figure 15. Estimation of pulmonary artery pressure.

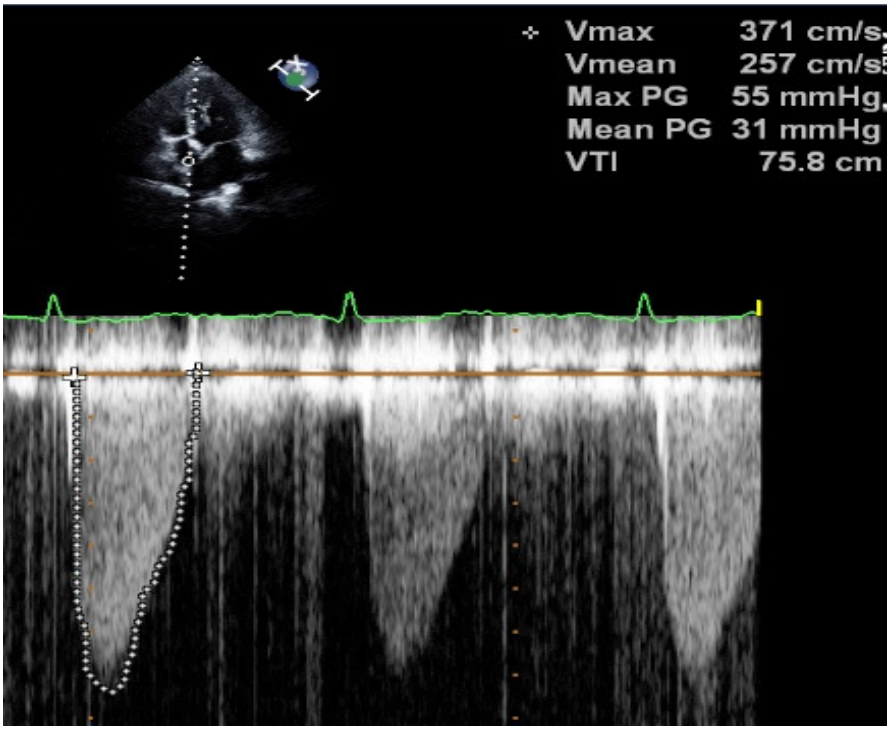


Figure 16. Measurement of size of main pulmonary artery

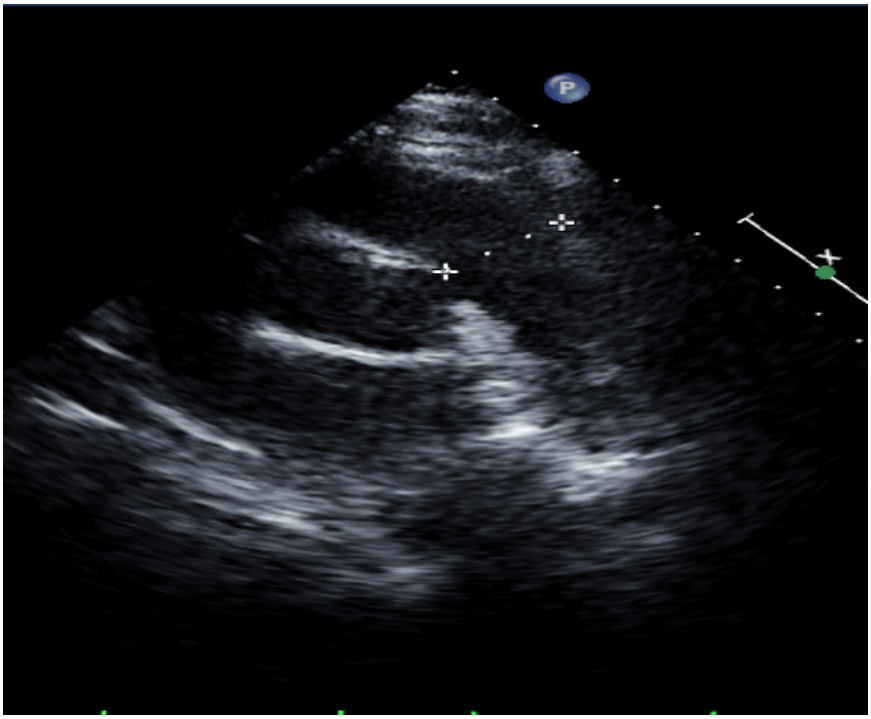


Figure 17. Measurement of right and left pulmonary artery size.

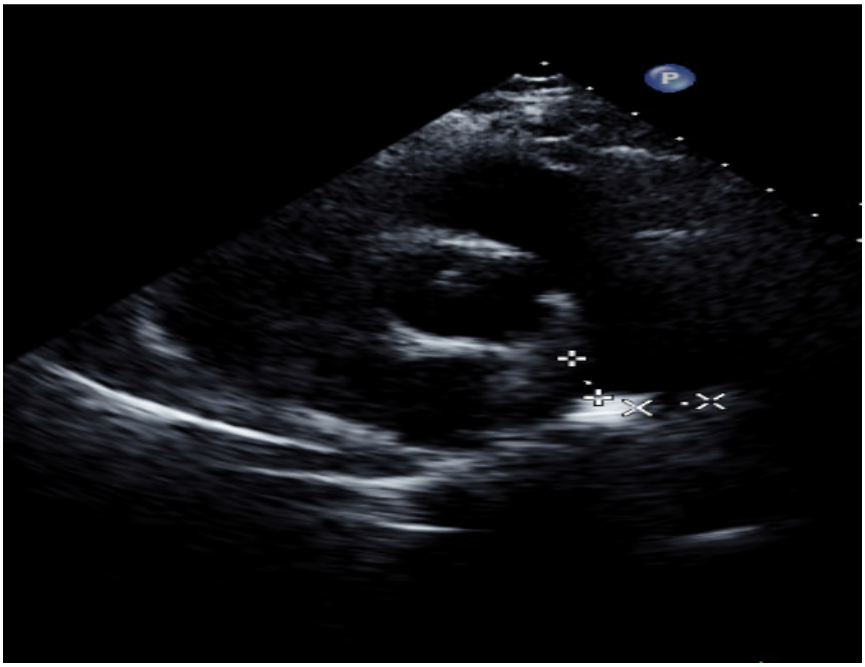


Table 13. Comparing duration of disease with pulmonary hypertension

Duration of disease	Subjects with PH
Less than 5 years	10
More than 5 years	4

(‘ P’ value = 0.125)

Heart valves:

Normal heart valves were found among 33(82.5%) subjects of our study population. The most frequent valve changes were age related sclerosis of aortic valve noted in 7(17.5%) subjects.

Table 14. Distribution of valve status.

Valves	No of patients	Frequency
Normal	33	82.5%
Age related Aortic sclerosis	7	17.5%

Right ventricle wall thickness(RVT):

The mean RVT was 0.68 ± 0.13 cm. Twelve() subjects with PH had RVT > 0.5cm and 2 subjects with PH had RVT < 0.5cm. The presence of pulmonary hypertension does not correlate with the thickening of right ventricular wall '(P' value = 0.232).

Table 15. Correlation of Right ventricle Thickness with pulmonary hypertension

RVT	Pulmonary hypertension (n =14)
< 0.5 Cm	2
>0.5 Cm	12

Figure 18. Comparison of Right ventricle Thickness with pulmonary hypertension

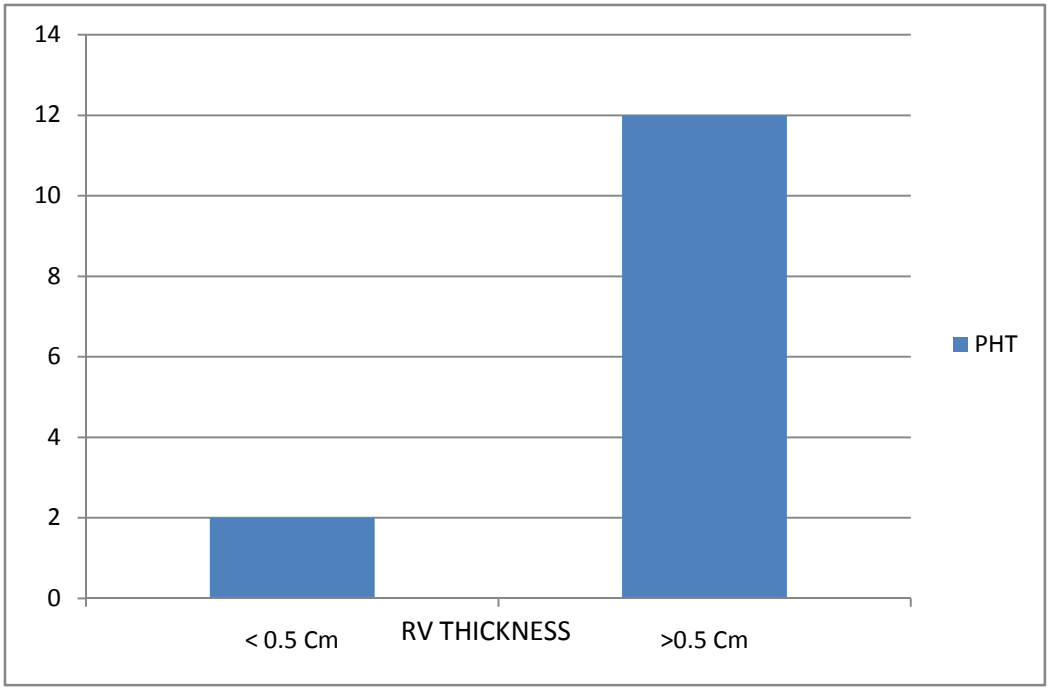
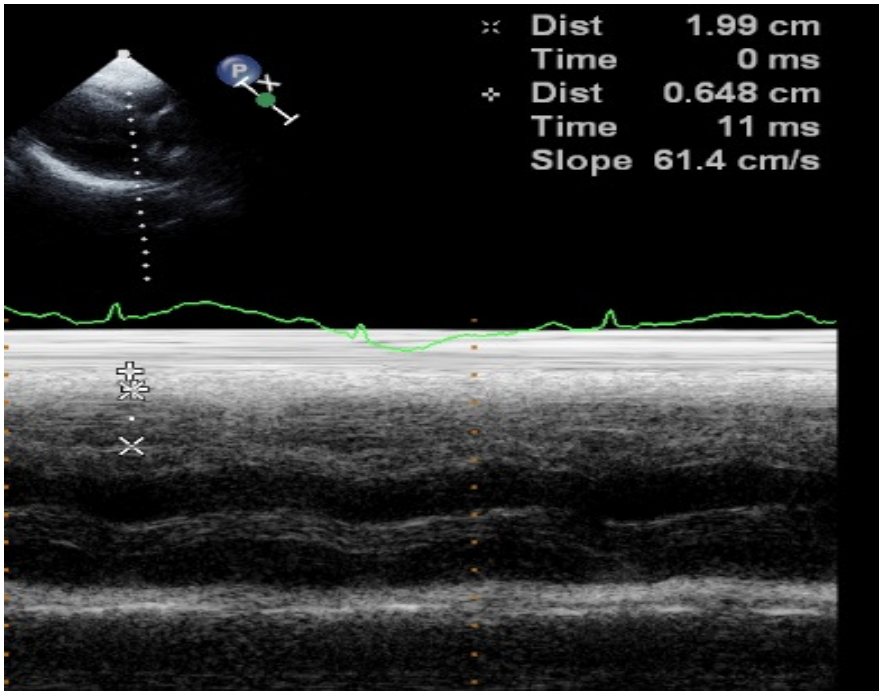


Figure 19. Measurement of Thickness and diameter of right ventricle



Left ventricle Diastolic dysfunction(LVDD):

LVDD was found in 14(35%) subjects of the study population. We studied the distribution of LVDD among subjects in relation to severity of airway obstruction. LVDD was noted in 1(33.3%) of mild COPD, 4(23.5%) of moderate COPD, 8(53.3%) of severe COPD and 1(20%) of very severe COPD subjects. There was no significant correlation between the severity of COPD and LVDD ('P' value of 0.296).

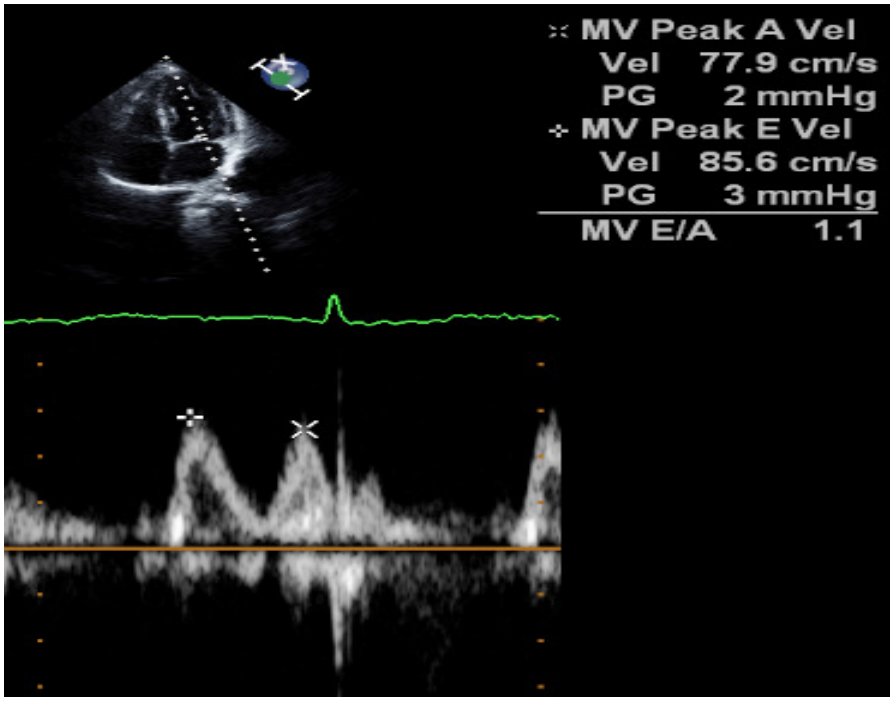
Table 16. Comparison of severity of airway obstruction with LVDD

Severity of obstruction	Patients with LVDD
Mild	33.3%
Moderate	23.5 %
Severe	53.3 %
Very severe	20%
	P = 0.296

ECHO FINDINGS AMONG STUDY POPULATION:

The mean ejection fraction among the subjects was 62.27 ± 3.08 %.The diameter of left ventricle during systole and end diastole were normal with mean value of 2.7577 ± 0.2621 cm and 4.1508 ± 0.4336 cm respectively.

Figure 20. Measurement of E/A ratio to assess LV Diastolic function



The diameter of right ventricle in all subjects were normal with mean 2.563 ± 0.46 cm. None of them had corpulmonale. Right ventricular hypertrophy defined by RV wall thickness was present in most of the study population with a mean value of 0.6842 ± 0.1344 cm. RV Systolic function assessed by TAPSE showed good right ventricular systolic function with mean of 1.9618 ± 0.2161 cm/sec. The IVC diameter was measured by subcostal view and the mean diameter was 1.18 ± 0.23 cm. IVC collapsed well in all patients during inspiration.

Figure 21. Measurement of left ventricle parameters

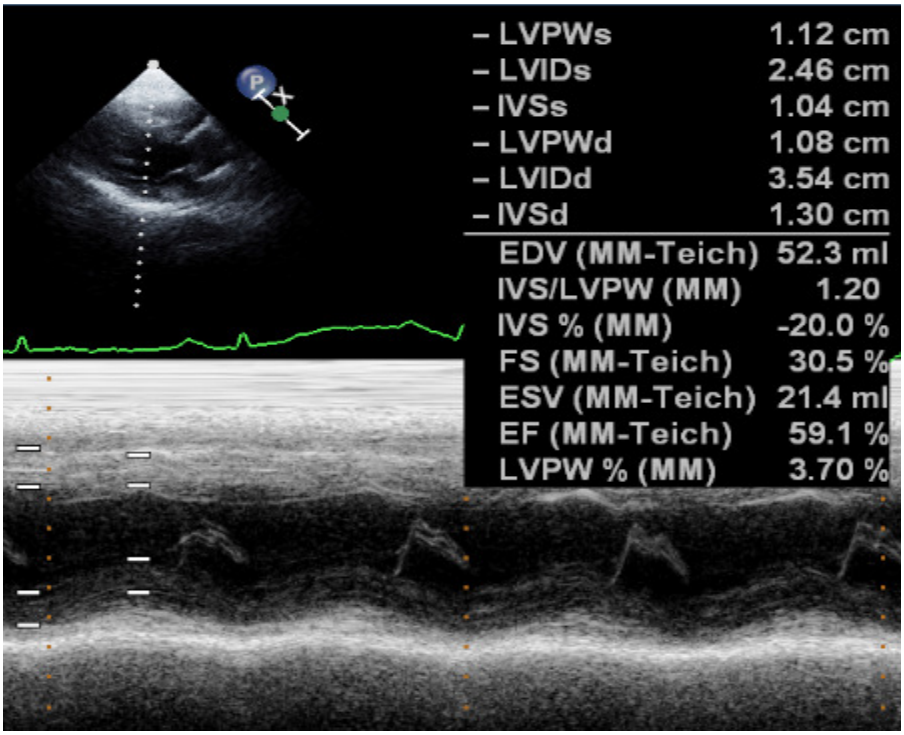


Figure 22. Measurement of IVC size

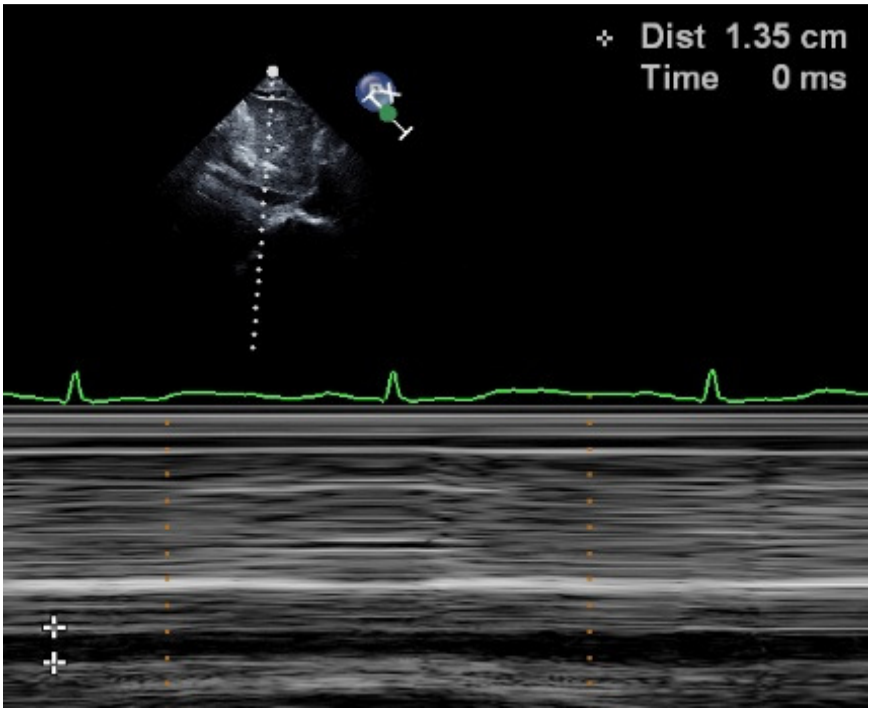
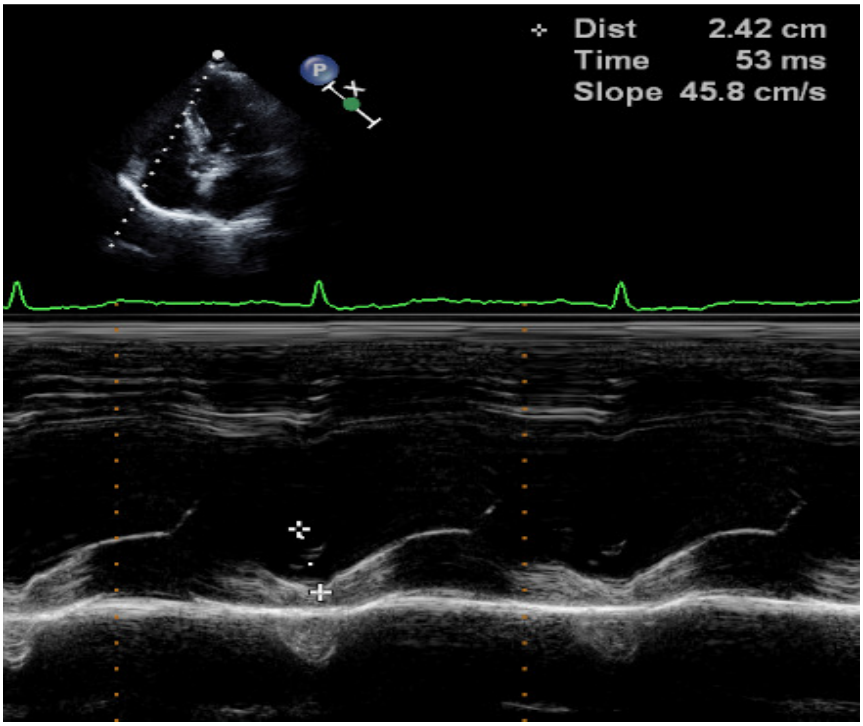


Table 17 . ECHOCARDIOGRAPHIC FINDINGS AMONG STUDY POPULATION.

S.No	Parameter	Mean ± SD
1.	Left ventricle internal diameter during systole (LVIDs) in cm	2.75 ± 0.26
2.	Left ventricle internal diameter during diastole (LVIDd) in cm	4.15 ± 0.43
3.	Right ventricle internal diameter in cm	2.563 ± 0.46
4.	Tricuspid Annular plane Systolic excursion(TAPSE) in cm	1.96 ± 0.21
5.	Right ventricle thickness in cm	0.68 ± 0.13
6.	Ejection fraction in percent	62.27 ± 3.08
7.	Interventricular septum in cm	1.25 ± 0.24
8.	Inferior vena cava in cm	1.18 ± 0.23

Figure 23. Measurement of TAPSE



3.CORRELATION OF VARIABLES BETWEEN PH AND NON PH GROUP

We divided the study population into two groups – PH group and non PH group and compared a set of variables like Age, BMI, Smoking pack years, duration of disease specific symptoms, lung function variables.

BMI and pack years were statistically significant between the two groups with a 'P' value of 0.030and 0.040 respectively. The subjects in PH group had lower BMI with mean of 19.8271 kg/m^2 compared to the subjects in non PH with mean of 22.3115 kg/m^2. The subjects in PH group had mean smoking of 54.07 ± 28.09 pack years which was statistically significant when compared to the non PH group subjects with mean of 37.76 ± 20.09 pack years with 'P' value of 0.040. The other variables like age, current

occupational status, co morbidities and duration of disease were not statistically significant between the two groups.

Table 18. Sociodemographic and disease specific variables among two groups.

Variables	PH group (mean ± SD)	Non PH group (mean ± SD)	'P' value
Age(in years)	64.14 ± 9.07	58.76 ± 9.23	0.085
BMI(in kg/m^2)	19.82 ± 2.59	22.31 ± 3.64	**0.030**
Smoking (in Pack years)	54.07 ± 28.09	37.76 ± 20.09	**0.040**
Duration (In years)	5.07 ± 3.09	6.19 ± 3.78	0.349

Comparison of disease specific variables:

In non PH group, 13(81.2%) subjects had grade 1 dyspnoea while the PH group had 3(18.8%) of subjects. The severity of dyspnoea between the groups was not statistically significant. The co morbidity profile between the groups were compared and found that diabetes and systemic hypertension were the most common comorbidity in both groups, but the distribution was not significant. There was no comorbidity among 36% of subjects in PH group and it was 64% in non PH group.

Table 19. Comparison of severity of dyspnoea among PH and non PH group

MMRC	PH group % of patients	Non PH group (mean ± SD)
Grade 1	18.8%	81.2 %
Grade 2	45%	55%
Grade 3	50%	50%

Table 20. Comparison of physiologic variables among PH and non PH group

Variables	PH group (mean ± SD)	Non PH group (mean ± SD)	'P' value
Post bronchodilator FVC(in litres)	2.08 ± 0 .60	2.34 ±0 .68	0.233
Post bronchodilator FEV1(in litres)	1.15 ± 0. 51	1.29 ± 0. .49	0.393
Post bronchodilator FEV1 (in percent)	49.57 ± 16.75	51.84 ± 16.01	0.676
6MWD(in metres)	465.71 ± 84.28	506.92 ± 91.37	0.171
Spo2 (in percent)	97.07 ± 1.26	97.34 ± 1.41	0.547

Table 21. Comparison of Echo variables among PH and non PH group

Variables	PH group (mean ± SD)	Non PH group (mean ± SD)	'P' value
TAPSE(in cm)	1.99 ± 0 .23	1.94 ± 0 .20	0.502
RVT (in cm)	0.68 ± 0.16	0.68 ± 0.11	0.929
RVID(in cm)	2.58 ± 0. .58	2.55 ± 0.39	0.863
IVC(in cm)	1.21 ± 0.30	1.17 ± 0.19	0.599
LVEI(in cm)	1.06 ± 0.10	1.08 ± 0.09	0.631
EF(in percent)	64.07 ± 3.26	61.30 ± 2.55	**0.005**
IVS(in cm)	1.29 ± 0.22	1.22 ± 0.26	0.400
LVIDd(in cm)	4.14 ± 0.30	4.15 ± 0.49	0.928
LVIDs(in cm)	2.69 ± 0.18	2.79 ± 0.29	0.251

There was no statistical significance between the PH and non PH group for the variables like FEV1, FEV1%, FVC, 6MWD, SPO2 and also for other echocardiographic variables except for ejection fraction.

Logistic regression analysis of variables between PH and non PH group:

The significant variables like BMI, Smoking pack years were further analysed by using multiple logistic regression. Both BMI and smoking pack years were adjusted for Age, Duration of disease and severity of COPD.

Table 22 .Logistic regression analysis of variables between PH and non PH group:

Variables	Adjusted odds ratio	95% confidence interval	'P' Value
BMI	0.76	0.59 – 0.98	0.04
Smoking pack years	1.024	0.99 – 1.05	0.13

BMI remained statistically significant with 'P' value of 0.04(adjusted odd's ratio of 0.76, 95% confidence interval 0.59 – 0.98). Smoking pack years lost its significance('P'value of 0.13, adjusted odd's ratio of 1.024, 95% confidence interval 0.99 – 1.05). We found that pulmonary hypertension was 0.76 times commoner in patients with low body mass index.

DISCUSSION

The important findings in our study were as follows

1. The mean post bronchodilator FEV1and predicted FEV1 in our study population were 1.24 ± 0.49 Litres and 51.05 ± 16.09% respectively.
2. The prevalence of pulmonary hypertension increased with the severity of COPD.
3. In stable COPD patients, the pulmonary hypertension were of mild grade.
4. By univariate analysis, COPD patients with pulmonary hypertension had lower BMI and had high smoking pack years than the patients without pulmonary hypertension with 'P' value of 0.030 and 0.040 respectively.
5. With Multiple logistic regression, BMI remained statistically significant with 'P' value of 0.04(adjusted odd's ratio of 0.76, 95% confidence interval 0.59 to 0.98).

COPD is primarily characterized by the presence of airflow limitation . It is well known that COPD extends beyond the lung and has several systemic manifestations. These manifestations/Co morbidities further impair functional capacity and health-related quality of life. Cardiovascular disease is the most frequently recognized co morbidity among COPD patients.The aim of our study was to evaluate the clinicophysiological characteristics of COPD and correlate them with the echocardiographic findings. The mean post bronchodilator FEV1and predicted FEV1 in our study population were 1.24 ±

0.49 Litres and 51.05 ± 16.09% respectively. We found 35%(n=14) of the stable COPD had mild pulmonary hypertension. None of the patient had severe pulmonary hypertension. The distribution of pulmonary hypertension among mild, moderate, severe and very severe COPD were 33.3%, 26.7%, 35.3% and 60% respectively. Left ventricle Diastolic dysfunction(LVDD) was found in 35% of the study population. Right ventricular free wall thickness more than 0.5cm was found in 92.7%(n=37) of patients and none of them had features of corpulmonale.

Sociodemographic characters:

In our study, 100 % of the subjects were males. Jindal SK et al and Buist AS et al[86] reported COPD more in men than women because of the difference in smoking habits. Similarly both male:female and smoker:non smoker ratios in india are not as high as in the western population, because of exposure to biomass fuels among women.The prevalence as per the INSEARCH 1 study (2006) which included 35,295 subjects were 5% in males and 3.2% in females[87].

The mean age of patients in our study was 60.65 ± 9.42 years. This was similar to a study by Hilde et al with 98 COPD patients with mean age of 62 ± 8 years[55]. In our study, 70% were currently employed and 32% were unemployed. The mean BMI of the study group was 21.44 ± 3.49 Kgs/m^2. 20% of patients had underweight. Low BMI in COPD is an independent risk

factor for increased mortality. Low BMI patients also have poor quality of life and increased risk of exacerbation[84]. A study by Maurizio et al[82] evaluated COPD patients of specific phenotype D and pulmonary hypertension, showed significant correlation between pulmonary hypertension and BMI. Kadam et al[84] in their study with 30 stable COPD patients showed that pulmonary hypertension had no correlation with BODE index. Socioeconomic status was assigned according to AICPI(IW) –May 2013 and in our study major proportion(75%) belonged to class 2 and class 3, while class 4 and class 5, in total had only 10%. A study by Merja et al on asthma and COPD patients showed that basic educational level remained an independent risk factor for COPD and the low household income was a risk factor for asthma. Poor socioeconomic status is a well documented risk factor in COPD probably due to overcrowding and exposure to smoke[1]. Our study subjects had mean smoking pack years of 43.47 ± 24.16 pack years and 87.5% had more than 20 pack years while 12.5% had less than 20 pack years. This result was almost similar to the study by Sultan et al , in which the mean pack years was 49.5 ± 22.2 pack-years[57] .

Physiological variables:

The mean FEV1 among our study population was 1.243 ± 0.49 litres , the mean FEV1 % predicted was 51.05 ± 16.09 % and the mean FVC was 2.25 ± 0.66 litres. Three subjects (7.5%) had mild disease, Moderate obstruction was present in seventeen subjects (42.5%), severe obstruction was

noted in fifteen patients(37.5%), underlying very severe COPD was diagnosed in five subjects (12.5%) . In our study most of the patients(80%) had moderate to severe COPD. The mean six minute distance in our study was 492 ± 90 meters. Schoos et al[58] in their study titled Echocardiographic predictors of exercise capacity in COPD had recorded the distance walked during six minutes among 90 patients and the mean distance was 403 ± 113 meters. In our study, three patients walked less than 350 meters and all had very severe COPD.

Jose M. Marin et al[76], in 2001, showed positive correlation between mean 6MWDand FVC, FEV1. Ameri et al[79] found positive correlation for six minute walk distance with diffusion capacity of carbon monoxide, Forced vital capacity and Forced expiratory volume in first second. Among them diffusion capacity correlated strongly with six minute walk distance, followed by Forced vital capacity and FEV1. Safwat et al with thirty COPD patients found strong association between predicted percentage of FEV1 and six minute walk distance with a ' r ' value of 0.77 and 'p' value less than 0.01)[77]. Nishiyama et al showed similar relation between six minute walk distance and spirometric values with $r = 0.70$ and $P < 0.0001$[78]. Our study results showed significant correlation between six minute walk distance and FEV1 in concordance with the above studies. But a study by Kodavala et al[80] in 45 COPD patients to find the correlation between 6MWD and severity of obstruction showed weak correlation (r= 0.280), without statistical significance between six minute walk

distance to forced expiratory volume in first second with 'p' value of 0.062 and forced vital capacity with ' p' value of 0.055. Six minute walk distance did not correlate with parameters like smoking score, BMI, age and baseline arterial partial pressure of carbondioxide. Similarly, Elie Fiss et al[81] found significant correlation was found between six minute walk distance and mean predicted forced vital capacity percentage and vital capacity but not for Inspiratory capacity and FEV1. These studies did not include patients with all grades of severity.

Echocardiographic variables:

RV Systolic function assessed by Tricuspid annular plane systolic excursion(TAPSE) showed good right ventricular systolic function with mean of 1.9618 ± 0.2161 cm/sec. There was no correlation between TAPSE and exercise capacity assessed by six minute walk distance. Our study finding was similar to the observation by Schoos et al , who showed TAPSE does not correlate with exercise capacity[58].

LVDD in our study population was 35%. LVDD was noted in 33.3% of mild COPD, 23.5% of moderate COPD, 53.3% of severe COPD and 20% of very severe COPD. There was no significant correlation between the severity of COPD and LVDD. Left ventricular diastolic dysfunction had been documented in COPD with varying prevalence. The right and left ventricle share a common interventricular septum(ventricular interdependence).The increase in LV end

diastolic pressure due to bulging of septum into left ventricle and increased afterload due to increase in intrathoracic pressure were the proposed mechanism[44]. A study by Cuttica et al found 54% prevalence of LVDD in COPD patients. Schoos et al found LVDD in 66% of COPD patients . They showed that LVDD was not significantly associated with exercise capacity (P = 0.278) [73]. Abroug F et al [48] in their study found 32% of patients with LVDD. Caram et al from their study with 25 mild/moderate COPD and 25 severe/very severe COPD patient found mild left diastolic dysfunction among 88% of patients irrespective of COPD severity [49].Boussuges et al. found a prevalence of 76% vs. 35% of LVDD in COPD patients compared to controls [50]. The higher prevalence rate found in the above studies was possibly due to enrollment of patients during exacerbation. We had more stringent selection criteria excluding patients with exacerbation within two weeks prior to recruitment. This criteria ruled out any transient dynamics in cardiac function during exacerbations.

Right ventricular hypertrophy defined by RV wall thickness more than 0.5 cm was present in most(92.7%) of the study population with a mean value of 0.68 ± 0.13 cm and prevalence of right ventricular hypertrophy both in pulmonary hypertension and non pulmonary hypertension group were comparable. Hilde et al[55] analysed the structure and function of right heart in COPD patients with normal pulmonary artery pressure and found that patients

with Right ventricular hypertrophy were more in the pulmonary hypertension group comparing the non PH group.

The measurable tricuspid regurgitation in our study population was found in 50% of the subjects. Among those with measurable TR, significant pulmonary hypertension was noted in 70% of subjects(35% of total subjects). In our study the distribution of pulmonary hypertension among mild, moderate, severe and very severe COPD were 33.3%, 26.7%, 35.3% and 60% respectively. Sultan et al[57] found Tricuspid regurgitation (TR) jet in 70.9% of patients with COPD. Increased pulmonary artery systolic pressure was noted in 51% of patients with TR (36% of total patients). Burgess et al noted TR in 68% of patients with COPD[61]. Gupta et al[44] found TR in 67.5% of study population and significant pulmonary hypertension was shown to be present in 63%.

In our study, the prevalence of pulmonary hypertension was 35%. According to severity of COPD, three subjects (7.5%) had mild disease, Moderate obstruction was present in seventeen subjects (42.5%), severe obstruction was noted in fifteen patients(37.5%), underlying very severe COPD was diagnosed in five subjects (12.5%) . In our study most of the patients(80%) had moderate to severe COPD. N.K.GUPTA et al [44] evaluated 40 COPD patients with echocardiography and found pulmonary hypertension among 63% (n=17). Among their 40 COPD subjects, 45% had mild COPD, while moderate, severe and very severe COPD were 27.5% , 12.5% and 15%

respectively. A study by Higham et al on the utility of echocardiography in assessing pulmonary hypertension secondary to COPD showed a prevalence of 55% among their study subjects. Their study had 16% of mild COPD, 26% of moderate COPD and 57% of severe COPD The majority of subjects(83%) in their study had moderate to severe COPD. Our study results were comparable to the study by Higham et al[45].

The pulmonary pressure in COPD patients had shown to increase 0.4 to 0.6mm Hg per year. This finding illustrate that pulmonary hypertension in COPD progress slowly[68]. In our study, the distribution of pulmonary hypertension among mild, moderate, severe and very severe COPD were 33.3%, 26.7%, 35.3% and 60% respectively. A recent small cohort reported that the frequencies of PH in mild, moderate, severe, and very severe COPD were 16.67 %, 54.55 %, 60.00 %, and 83.33 %, respectively[44]. In another study, the frequency of PH was also found to be 25 %, 43 %, and 68 % in mild, moderate, and severe COPD, respectively[62].Fayngersh V et al studied the prevalence of PH in 105 stable COPD patient and found 60% (n=63) of patients with pulmonary hypertension. In their study, there was a significant association between FEV1 and pulmonary hypertension. COPD patients with PH had lower FEV1% predicted than the patients without pulmonary hypertension(51.8 ± 18.8 vs. 62.7 ± 20.5%, P = 0.006)[69] . In 2002, Scharf et al[70] studied the hemodynamic characterization in patients with emphysema. They showed that COPD patients

with pulmonary hypertension had lower FEV1 compared to those without FEV1 which was statistically significant. Mammosser et al[31] in their study on COPD patients to assess pulmonary hypertension enlightened that subjects with pulmonary hypertension had lower FEV1 than those without pulmonary hypertension. The study by Higham et al[60] in assessing the pulmonary artery pressure by echo found significant association between severity of COPD and pulmonary hypertension(r = -0.26, P = 0.05). Bishop et al[71] used different non invasive techniques in predicting pulmonary artery pressure including echocardiography and found no correlation between severity of COPD and pulmonary hypertension. Our study results were in partial agreement with the above mentioned studies. The prevalence of pulmonary hypertension in severe and very severe COPD were high compared to mild and moderate COPD. In our study, the higher percentage of pulmonary hypertension found in mild COPD patients(33.3%) might be due to less number of COPD patients in that group(n=3). None of them had severe pulmonary hypertension. Severe pulmonary hypertension in COPD was reported very rare. Thabut et al[32] reported only 1 to 3 % of severe PH among COPD patients. Gupta et al[44] study had 17.65% of severe pulmonary hypertension among COPD patients. We included only the stable COPD patients and those without other coexisting lung disease. The studies mentioned above excluded the patients with other lung diseases but not those with exacerbation .

With respect to exercise capacity and pulmonary hypertension, in our study only 14% with pulmonary hypertension covered less than 350 meters, where as 86%(n=12) with PHT walked more than 350meters. Cuttica MJ et[72] al in their study on non severe COPD patients, evaluated right heart changes in predicting exercise capacity and showed that mild pulmonary hypertension was a poor predictor of exercise capacity. Boerrigter BG[73] et al studied the ventilatory and cardiocirculatory exercise profiles in COPD and found that exercise capacity was limited only in COPD patients with severe pulmonary hypertension. Our study results were concurent with that of Cuttica et al and Boerrigter et al.

By univariate analysis, statistically significant difference was observed for smoking pack years between COPD patients with pulmonary hypertension and COPD patients without pulmonary hypertension(Unadjusted odds ratio 1.03; 95% confidence interval 1.0 – 1.061; 'P' value = 0.05). However the relationship did not withstand adjustment with confounding factors like age, duration and severity of COPD(Adjusted odds ratio 1.021; 95% confidence interval 0.98 – 1.056; 'P' value = 0.20). COPD patients with pulmonary hypertension had lower BMI when compared to those without pulmonary hypertension which was statistically significant(19.82 ± 2.59 Vs 22.31 ± 3.64, 'P' value = 0.030). On multiple logistic regression analysis, this relationship withstood adjustment with confounders like age, severity of COPD

and duration (adjusted odd's ratio of 0.76, 95% confidence interval 0.59 – 0.98, 'P' value of 0.04). A study by Maurizio et al[82] evaluated COPD patients of specific phenotype D and pulmonary hypertension, showed significant correlation between pulmonary hypertension and BMI. Our study results were similar to the study by Maurizio et al. But, Kadam et al[84] in their study with 30 stable COPD patients compared the severity of obstruction with pulmonary hypertension and osteoporosis. They found that pulmonary hypertension correlated with FEV1 but not for BODE index(P = 0.88). Their study did not include all grades of severity. Similarly, Joppa et al[85] studied 43 COPD patients of which 14 were females, to find the predictors of pulmonary hypertension. There was no statistical significant difference in BMI between the patients in pulmonary hypertension and non pulmonary hypertension group (22.9 ± 6 vs 24.6 ± 5.6, P = 0.352). Their study had 30% female population, 11% non smokers and none of them had biomass exposure and included COPD with different etiological profile.

We found that patients with low BMI have 24% less chance for developing pulmonary hypertension.

SUMMARY

Forty patients diagnosed as COPD without other lung disease and without primary cardiac disease had been included in the study. We evaluated the clinicophysiological characters like exercise capacity, lung function variables and correlated them with echocardiographic parameters like pulmonary hypertension, ventricular dimension and systolic, diastolic functions. All the participants were males with mean BMI of 21.44 ± 3.49 kg/m^2. When socioeconomic status was considered, major proportion were above class 3.The mean post bronchodilator FEV1and predicted FEV1 in our study population were 1.24 ± 0.49 Litres and 51.05 ± 16.09% respectively. The mean distance covered by our subjects during six minute walk test was 492 ± 90 metres. There was significant correlation between severity of COPD and exercise capacity assessed by six minute walk distance. We found a prevalence of 35% pulmonary hypertension among our study population. The prevalence of pulmonary hypertension increased with the severity of COPD. Left ventricle diastolic dysfunction was noted in 35% of the subjects. We divided the study population into two groups – COPD patients with pulmonary hypertension and COPD patients without pulmonary hypertension and compared variables between these two groups. By univariate analysis, statistically significant difference was observed for smoking pack years between COPD patients with pulmonary hypertension and COPD patients without pulmonary hypertension. However the relationship did not withstand adjustment with confounding

factors like age, duration and severity of COPD.COPD patients with pulmonary hypertension had lower BMI when compared to those without pulmonary hypertension which was statistically significant. On multiple logistic regression analysis, this relationship withstood adjustment with confounders like age, severity of COPD and duration (adjusted odd's ratio of 0.76, 95% confidence interval 0.59 – 0.98, 'P' value of 0.04). We found that patients with low BMI have 24% less chance for developing pulmonary hypertension.

CONCLUSION

Our study showed that prevalence of pulmonary hypertension increased with severity of COPD. Severe pulmonary hypertension was not observed in our study with stable COPD patients. Right ventricle hypertrophy and diastolic dysfunction of left ventricle were the other common findings in COPD patients. Since cardiovascular disease is the major cause of morbidity and mortality in COPD, it is essential to evaluate the cardiac status at the time of initial diagnosis. The overall survival and quality of life can be improved by addressing this comorbidity.

LIMITATION

1. Forty samples were included in the study due to time constraints.
2. Our study did not have female COPD patients.
3. The sample distribution based on severity of COPD was unequal.
4. Exact pulmonary pressure as measured by right heart catheterization cannot be obtained from echocardiography.
5. Genetic factors known to be associated with pulmonary hypertension were not analysed in our study.

RECOMMENDATION

1. Studies with larger sample size and involving different ethnicity are needed.
2. Uniform distribution of sample is needed to increase the credibility of the study.
3. Genes associated with pulmonary hypertension need to be incorporated in future studies.

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MASTER CHART CODING SHEET

OP NO – Outpatient number

AGE in years

BMI in Kg/m^2

Socio – Socioeconomic class(1- class 1)

employ – Employment status(Y –Employed, N - Unemployed)

Duration – Duration of disease(in years)

exacerb –Number of exacerbation in the previous year

comorbi – Comorbidities(0 – no comorbidities, 1 – systemic hypertension, 2 – Diabetes, 3 – CVA, 4 -GERD)

Mmrc in grades

FVC, FEV1 in litres

FEV1% in percentage

6MWD in metres

SPO2 in percentage

TR – significant jet(0- absent, 1- present)

PH-(0- absent, 1- present)

PAP in mmHg

LVDD-(NO-absent, Y- present)

LVEI in ratio

EF in percentage

OBSTRU- severity of COPD

TAPSE, RVT,RVID,MPA,RPA,LPA, IVIDd, LVIDs, IVS,IVC in centimetres

S.NO	OP NO	AGE	BMI	Socio	employ	pack yr	Duration	exacerb	comorbi	Mmrc	FVC	FEV1	FEV1%	6MWD
1	13047011	55	22.8	2	Y	50	2	0	4	1	3.34	2.16	88	580
2	13032651	64	16.5	5	N	30	5	1	0	3	2.28	0.82	35	370
3	13011190	61	20.08	4	Y	79	10	1	0	2	2.05	1.22	64	550
4	13087290	65	16.4	1	Y	96	3	1	0	2	1.91	0.87	48	580
5	13085849	71	15.4	4	N	70	3	0	2	2	1.65	0.9	51	400
6	13092026	50	19.3	3	N	37	3	1	4	3	2.88	1.21	46	450
7	12041260	74	27.1	2	N	52	2	0	0	1	2.09	1.2	55	640
8	3045869	56	26.8	3	N	27	15	1	3	2	2.14	0.81	49	430
9	14023282	62	18	3	Y	46	10	0	0	2	2.22	0.95	49	550
10	13045496	65	23	3	Y	47	2	1	2	2	2.7	2.5	62	360
11	10050186	54	25	2	Y	36	6	0	0	1	2.63	1.43	51	490
12	12072501	55	24.8	1	Y	40	4	1	4	2	1.81	1.15	47	570
13	14003763	65	24.9	1	Y	19	10	1	2	2	2.01	0.99	40	490
14	13053833	60	17.3	3	N	32	1	1	0	1	2.66	1.61	64	540
15	14029559	70	22	2	Y	47	5	0	1,2	2	2.88	1.07	59	540
16	14020105	40	21	2	Y	22	7	1	0	1	3.29	1.78	54	560
17	14016404	48	19.6	2	N	28	1	0	0	2	3.34	1.91	68	400
18	14033617	53	27.2	2	Y	29	4	0	2	1	2.25	1.48	55	470
19	6061352	64	23.3	2	Y	40	7	1	1	2	1.41	0.62	26	430
20	11013141	56	20	2	Y	35	6	0	0	1	2.11	1.19	58	570
21	14045546	71	28.4	2	N	72	4	0	1	2	2.54	1.64	69	430
22	14046148	55	17.2	3	Y	37	2	0	0	1	2.57	1.53	57	550
23	2045192	48	24	2	Y	22	10	1	0	2	3.58	2.08	73	570
24	7021257	64	23.3	1	Y	22	4	0	1,2	2	1.94	0.88	36	430
25	5052433	57	14.7	3	Y	40	5	2	1	3	1.04	0.35	30	410
26	8083168	71	21.2	4	N	110	6	2	0	2	1.27	0.49	22	320
27	13090284	80	20.1	1	Y	10	1	1	0	1	2.63	1.71	88	490
28	14048517	77	22.9	2	N	30	10	0	3	2	1.25	0.94	44	440
29	14049976	50	20	3	Y	10	10	2	0	2	1.92	1.21	56	490
30	11063165	58	19	2	Y	60	6	1	0	1	2.31	1.15	43	450
31	13073673	70	16.9	2	Y	67	5	2	0	2	1.22	0.64	29	350
32	12052274	67	23.4	2	Y	42	5	1	1,2	1	2.38	1.11	40	560
33	14026262	75	20.8	2	Y	75	10	3	0	3	1.13	0.51	29	330
34	4041711	60	25.5	2	N	10	10	1	2	1	2.81	1.66	64	640
35	12034934	42	19	2	Y	29	1	0	0	1	1.99	1.61	55	500
36	9082672	63	19.9	2	Y	46	10	1	0	2	1.92	0.87	31	560
37	11027745	61	24.4	2	Y	38	8	0	1	1	2.75	2.18	81	470
38	14061921	55	19.7	2	N	100	5	2	0	2	1.79	1.06	39	440
39	14037509	48	25.3	2	Y	20	2	1	0	1	1.86	1.01	37	690
40	9079223	66	21.5	3	Y	37	12	2	4	1	3.51	1.39	50	610

SPO2	TR	PH	PAP	TAPSE	RVT	RVID	LVDD	MPA	RPA	LPA	LVIDd	LVIDs	IVS	LVEI	EF	VALVES	IVC	OBSTRU
99	0	0	0	1.9	0.77	1.92	NO	1.96	1.1	1.2	3.8	2.66	1.14	1.03	60	N	1.3	MILD
95	0	0	0	1.78	0.87	1.99	NO	3.04	2.64	2.3	4.5	3	1.31	1	63	N	1.7	SEV
97	1	1	45	2.4	0.5	1.99	NO	2.4	1.1	1.24	4.28	2.85	0.907	1.02	62	AS,AR	1.3	MOD
98	1	1	35	1.81	0.567	1.89	NO		1.37	1.39	4.17	2.66	1.02	1	66	N	1.04	SEV
98	1	1	37	1.86	0.68	1.99	NO	1.8	1.1	1.2	3.54	2.46	1.04	1.06	59	N	0.8	MOD
98	1	1	35	1.52	0.957	2.19	Y	2.06	1.19	1.46	3.99	2.76	1.24	1	59	N	1.5	SEV
96	1	0	24	1.79	0.731	3.18	NO	1.6	1.15	1.21	5.12	3.32	1.24	1.1	64	N	1.38	MOD
97	0	0	0	1.7	0.9	2.9	Y	1.3	0.9	1.14	4.03	2.77	1.09	1.2	60	AR	1.3	SEV
98	1	0	20	1.99	0.84	2.7	NO	1.28	1.09	0.8	4.2	2.8	1.2	1.22	63	AS,AR	1.4	SEV
97	1	1	40	1.9	0.6	2.66	NO	1.18	0.96	0.68	4.1	2.8	1.3	1.29	60	AS	1.15	MOD
98	1	0	25	1.96	0.581	2.86	NO	1.21	0.833	0.928	3.92	2.62	1.4	1.37	62	N	1.2	MOD
94	0	0	0	1.9	0.56	2.59	Y	1.11	1.04	1.02	4.78	3.32	0.84	1.02	58	N	0.8	SEV
98	0	0	0	1.97	0.57	2.5	NO	1.9	0.93	0.64	3.98	2.71	1.67	1.02	60	N	1.19	SEV
98	0	0	0	1.52	0.735	2.85	NO	1.92	0.7	0.93	4.41	2.98	1.21	0.97	60	N	1.04	MOD
98	1	1	45	1.79	0.66	3.24	Y	1.97	0.99	1.25	4.43	2.91	1.52	0.976	63	N	1.23	MOD
98	0	0	0	1.97	0.605	2.82	NO	1.24	1.04	0.69	4.03	2.67	1.41	1.01	63	N	1.15	MOD
97	0	0	0	1.97	0.605	2.03	NO	1.51	0.877	0.961	4.45	2.9	1.17	1.02	64	N	0.979	MOD
97	0	0	0	2.14	0.576	2.36	NO	1.5	1.02	1.07	4.9	3.17	1.27	1.1	64	N	1.31	MOD
98	1	1	49	2.12	0.922	3.34	NO	1.36	0.758	0.938	4.03	2.59	1.33	1.02	65	N	1.61	VERY
98	0	0	0	2.12	0.706	2.27	Y	1.24	0.698	0.77	4.03	2.67	0.857	1.12	63	N	0.922	MOD
97	0	0	0	1.99	0.73	2.98	NO	1.8	1.2	1.3	4.09	2.77	1.33	1.01	61	N	1.2	MOD
98	1	1	40	1.92	0.8	3.1	NO	1.4	1.1	1.3	4.45	2.68	1.56	1.1	70	N	1.24	MOD
98	0	0	0	2.19	0.55	2.47	NO	1.27	1.1	1.15	4.49	3.02	1.21	1.01	61	N	1.08	MOD
98	0	0	0	1.96	0.634	3	Y	1.62	1.02	1.22	3.92	2.69	2.15	1.05	59	N	1.08	SEV
98	1	0	25	1.97	0.735	2.53	NO	1.31	0.634	0.779	3.76	2.57	0.899	1.14	60	N	0.788	VERY
93	0	0	0		0.9	3.26	Y	1.84	0.893	1.1	3.09	2.19	1.07	1.2	57	AS	1.15	VERY
97	1	1	35	2.07	0.605	2.87	Y	1.6	0.97	1.01	3.98	2.52	1.11	1.02	67	AS	1.08	MILD
98	0	0	0	2.38	0.691	2.07	Y	1.81	0.824	0.991	3.68	2.57	1.21	1.01	58	N	1.19	SEV
98	1	1	30	2.37	0.872	2.91	NO	1.48	0.624	0.974	4.51	2.86	1.16	1.31	66	N	1.65	MOD
98	0	0	0	2.08	0.69	2.47	NO	1.4	0.8	1.1	4.51	2.96	1.02	1.01	63	N	1.23	SEV
94	1	1	35	1.92	0.572	2.7	NO	1.34	0.864	0.993	4.29	2.7	1.55	1	67	N	0.926	VERY
96	1	1	43	1.99	0.84	3.42	Y	1.27	1.03	1.11	4.05	2.59	1.46	1.01	66	N	1.69	SEV
97	1	1	45	2.17	0.449	1.8	NO	1.29	0.527	0.908	3.63	2.33	1.51	1.1	64	AS	1.06	VERY
98	0	0	0	1.51	0.678	2.76	Y	1.29	1.05	1.1	4.75	3.2	1.16	1	61	N	1.15	MOD
98	0	0	0	1.64	0.613	1.96	Y	1.23	0.67	0.726	3.68	2.49	1.35	1.1	61	N	1.11	MOD
99	1	0	15	2.08	0.605	2.2	NO	1.3	0.804	0.82	4.45	3.02	1.21	1.21	60	N	1.15	SEV
98	0	0	0	2.25	0.655	2.52	NO	1.53	0.758	0.773	3.43	2.42	1.35	1.15	57	N	1.2	MILD
95	1	1	37	2.07	0.519	2.03	NO	1.38	0.882	0.935	4.54	2.98	1.47	1	63	N	0.788	SEV
98	0	0	0	1.85	0.844	2.98	Y	1.34	1.01	1.03	4.6	2.86	1.11	1.02	68	N	1.08	SEV
97	1	0	21	2.14	0.454	2.23	Y	1.23	0.996	1.04	3.44	2.27	1.06	1.01	64	N	1.38	SEV