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Assessment of Right and Left Ventricular Function in Patients with Chronic Obstructive Pulmonary Disease and Their Co-Relation with the Severity of Disease.

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ABSTRACT

The aim of this study was to evaluate both right ventricle (RV) and left ventricular (LV) function in patients with COPD by echocardiography and its correlation with severity of disease. Sixty two patients with COPD and twenty healthy subjects were assessed by echocardiography and pulmonary function test. LV parameters were similar in both groups while RV parameters were significantly different in COPD patients as compared to control group. LV diastolic dysfunction was significantly higher in COPD patients. Mild, moderate, severe, and very severe COPD were seen in 30.7%, 40.3 %, 22.5%, and 6.5% patients, respectively. Pulmonary hypertension (PH) was observed in 38.7% patients. Mild, moderate and severe PH were present in 45.8%, 41.7%, and 12.5% respectively cor pulmonale was observed in 41.9%, while RV and LV systolic dysfunction were present in 20.9% and 3.2% of all COPD patients respectively. There is high prevalence of pulmonary hypertension, cor pulmonale and right ventricular systolic dysfunction in COPD and severity increases with level of severity of COPD. Impairment of LV systolic function was rarely found, while LV diastolic function was very common.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has been variously labelled in the past as chronic bronchitis and emphysema, chronic nonspecific respiratory disease, chronic airway obstruction, chronic airflow limitation and chronic obstructive lung disease, depending upon the understanding of the pathophysiology and clinical features of the syndrome of chronic cough and/or airways obstruction. COPD is presently accepted as an overall common term for a variety of clinical disorders with chronic bronchitis at the one end and emphysema at the other end of the spectrum.

COPD is further defined by GOLD as a preventable and treatable disease with some significant extra pulmonary effects. Globally, COPD has emerged as the major cause of morbidity and mortality expected to become the 3rd most leading cause of death [1]. Cardiac manifestations are the most common extra pulmonary effects in COPD patients. It is generally known that dyspnoea and exercise tolerance reduction in COPD patients occur in the advanced stage of the disease as a result of progressive bronchial obstruction, and the development of pulmonary arterial hypertension [2]. In more advanced disease cardiovascular diseases account for 20%–25% of all deaths in COPD [3].

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In several studies, it has been shown that right ventricular pressure overload, as a consequence of the increase of pulmonary vascular pressure can affect the left ventricular filling profile diminishing its compliance by means of the interventricular septum interdependence [4-7]. Echocardiography provides a rapid, non-invasive and accurate method to evaluate both right ventricle and left ventricular function [8].

The aim of this study is to evaluate both left and right ventricular function in patients with COPD by echocardiography and its correlation with severity of disease.

MATERIALS AND METHODS

The present study was carried out at SRMS-IMS Hospital, Bareilly, Uttar Pradesh, India, after obtaining approval from the ethical committee of the institute, and informed written consents were obtained from all subjects.

Study Population

Sixty two patients (47 males and 15 females; mean age 60.9 ± 11.5 years) with COPD defined by American Thoracic Society classification and good echocardiographic image quality were enrolled from Chest Department of SRMS Institute of Medical Sciences, Bareilly, Uttar Pradesh. Patients with coronary artery disease, valvular heart disease, cardiomyopathy, hypertension, any systemic disease that can cause pulmonary hypertension, patients with poor echo window, and patients who were unable to perform PFT were excluded from the study. The control group consisted of 20 healthy subjects (15 males and 5 females, mean age 61.6 ±10.1years) with normal spirometry results.

All patients were subjected to routine investigations including complete blood count, lipid profile, blood sugar, blood urea, serum creatinine, electrolytes, liver function tests and electrocardiography.

Pulmonary Function Test

All patients underwent respiratory tests with body spiro-plethysmography. Forced vital capacity(FVC), forced expiratory volume(FEV1), and peak expiratory flow(PEFR) were measured and diagnosed and classified according to GOLD guidelines (post bronchodilator FEV_1 / FVC ratio < 70% of predicted), mild ($FEV_1 \geq 80\%$ of predicted), moderate ($50\% \geq FEV_1 < 80\%$ predicted), severe ($30\% \geq FEV_1 < 50\%$ predicted), and very severe ($FEV_1 < 30\%$ predicted), respectively.

Echocardiography

Examinations were performed with the SIEMENS echocardiography machine with 4 MHz transducer. Electrocardiographic monitoring was done in all patients. Echocardiography was reviewed to assess the pericardium, valvular anatomy and function, left and right side chamber size and cardiac function. Measurements and recordings were made by M-mode, 2 d -mode, colour flow mapping, and pulsed and continuous wave Doppler recordings were obtained for each subject.

Right ventricle dimension was measured by M-Mode echo and right ventricular dilation or cor pulmonale was said to be present when basal RV diameter was > 2.8 cm or mid RV diameter was > 3.3 cm. Right ventricle contractility was also noted and right ventricular systolic dysfunction was said to be present when RVEF was < 50%.

Tricuspid regurgitant flow was identified by colour flow Doppler technique, and severity was assessed with jet area: mild (4 cm^2), moderate (4-8cm^2), severe (>8cm^2). Maximum jet velocity measured by continuous wave Doppler was used for measurement of right ventricular systolic pressure.

The systolic pressure gradient between the right ventricle and right atrium was measured by calculating the maximum peak velocity by means of the Bernoulli equation. The right ventricular systolic pressure considered to be equal to the pulmonary artery systolic pressure in the absence of right ventricular outflow obstruction, was measured by adding to this gradient the estimated right atrial pressure. Mean Pulmonary Arterial Systolic Pressure (PASP in mmHg) = right ventricular systolic pressure = trans-tricuspid pressure gradient (TTPG) + right atrial pressure (RAP), where trans-tricuspid gradient is $4v^2$ (v = peak velocity of tricuspid regurgitation, m/s).[9] Right atrial Pressure (RAP) was estimated from the evaluation of the inferior vena cava during respiration. If the inferior vena cava diameter is normal and the segment adjacent to the right atrium collapses by at least 50% with respiration, then right atrial pressure is

estimated as 5 mm Hg. If the inferior vena cava diameter is normal but respiratory variation is less than 50%, right atrial pressure is estimated as 10 mm Hg; if the inferior vena cava is dilated and respiratory variability is less than 50%, right atrial pressure is estimated as 15 mm Hg; if both the inferior vena cava and the hepatic veins are dilated and there is no change in inferior vena cava size with respiration, right atrial pressure is estimated as 20 mm Hg [10].

Pulmonary hypertension (PH) was defined as peak systolic pressure greater than 30 mm Hg. PH was classified into mild, moderate, and severe category as PASP 30–50, 50–70, and >70 mmHg, respectively [11].

Left ventricular internal cavity dimensions, and septal and posterior wall thickness were measured. Similarly RV internal cavity dimensions, RV free wall thickness, right ventricular ejection fraction were also measured. All measurements were obtained on the basis of the standards of the American Society of Echocardiography [12].

Left ventricular function was also assessed by modified Simpsons method using end diastolic and end systolic volumes.

Transmitral flow velocities were recorded from the apical window, the following variables were measured: peak velocity of early diastolic filling (E), velocity of late filling with atrial contraction (A), E/A ratio, and deceleration time of E. The isovolumetric relaxation time (IVRT) was recorded from the apical 4-chamber view by simultaneous recording of the aortic and mitral flows. Left ventricular diastolic dysfunction (LVDD) is said to be present when E/A is <1.3 (age group 45–49 years), <1.2 (age group 50–59 years), <1.0 (age group 60-69 years), and <0.8 (age group ≥70 years) [13].

Statistical Analysis

The data were analyzed for both groups by using Microsoft Excel 2010 software. Mean ± SD was calculated and unpaired student's t-test was applied. P-value of ≤0.05 was considered as statistically significant, a value of ≤0.01 as very significant and a value of ≤0.001 as highly significant.

RESULTS

A total of 62 patients were recruited in our study. The clinical characteristics, haematological and biochemistry parameters are shown in Table 1. Age, sex, mean systolic, diastolic and mean blood pressure values in COPD patients and in the control group, were not significantly different. Sinus rhythm was present in ECG tracing in all patients. The heart rate (HR) in the COPD patients did not differ significantly from the control group. Haemoglobin was significantly higher in COPD group as compared to controls while all other haematological and biochemical parameters were not significantly different in both groups.

Table 1: Clinical and laboratory characteristics of the study population

Variable	COPD group n= 62	Control group n=20	P value
Mean Age (yrs)	60.9 ± 11.5	61.6 ±10.1	NS
Male (%)	75.8	75	NS
Female (%)	24.2	25	NS
Systolic BP (mmhg)	116.46 ±4.12	118.52 ±5.02	NS
Diastolic BP (mmhg)	76.8 ±3.34	77.2 ±3.68	NS
Mean BP (mmhg))	89.6 ±2.82	88.7 ±3.02	NS
Heart rate per min	76.8 ±7.43	77.3 ±6.93	NS
Blood sugar (mg%)	121.0 ±8.10	119.0 ±8.70	NS
Serum creatinine (mg%)	1.06 ±.12	1.03 ±.15	NS
Heamoglobin (g%)	17.4 ±1.36	12.9 ±2.39	< 0.05
Total leucocyte count	8600 ±1800	8400 ±1700	NS
ESR	10.6 ±2.32	10.45 ±2.61	NS
Serum Bilirubin (mg%)	.85 ±.32	.87 ±.33	NS

The spirometry results shown in Table 2 indicate bronchial obstruction in COPD patients (FEV1 65.31±20.26 %, FEV1/VC 51.31±20.26%) while no ventilation impairment was seen in the control group.

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Table 2: Spirometry analysis of study population

Variable	COPD group n=62	Control group n=20	P value
FVC (L)	2.4±0.90	3.05±0.47	0.02
FVC (%)	81.35±28.59	101.63±9.05	0.003
FEV1(L)	1.55±0.69	2.96±0.58	0.0001
FEV1 (%)	65.31±20.26	93.75±2.69	0.0001
FEV1/FVC (%)	51.31±20.26	86.58±6.22	0.001

FVC -Forced Vital Capacity, FEV1- Forced Expiratory Volume

Echocardiography dimensions of left and right cardiac chambers of the studied groups are shown in Table 3. Left ventricular end diastolic (LVD) and end systolic (LVS) diameters, interventricular septum thickness in diastole (IVS), LV posterior wall thickness (PWT) in diastole and left atrium diameter (LA) in COPD patients and control group were not significantly different . Right ventricular end diastolic diameter at base, diameter at mid cavity level , base to apex length, and diameter of right ventricular outflow tract (RVOT) above aortic and pulmonary valve level , right ventricular free wall thickness (RVWT) , pulmonary artery (PA) diameter and right atrial diameter (RA) were significantly higher in COPD patients than control group.

Table 3: Echocardiographic dimensions of left and right cardiac chambers.

Variable	COPD group n=62	Control group n=20	P value
LVD (mm)	42.5±5.9	42.0±5.3	0.8
LVS (mm)	23.5±4.4	23.3±2.09	0.5
IVS(mm)	10.39±0.7	10.5±1.07	0.5
PWT(mm)	10.16±1.13	10.1±0.7	0.8
LA (mm)	36.4±3.5	35.9±3.7	0.12
RV basal(mm)	35.2±6.76	25.9±2.03	0.0001
RV mid(mm)	36.7±7.68	30.1±1.4	0.0004
RV base to apex (mm)	52.9±21.8S	62.7±6.04	0.0001
RVOT above AV(mm)	31.3±6.25	27.6±1.54	0.001
RVOT above PV(mm)	26.6±5.9	20.1±0.93	0.0001
PA (mm)	24.4±4.7	20.6±0.82	0.001
RV W T (mm)	9.8±1.5	5.8±8.04	0.007
RA (mm)	42.8±8.8	35.8±1.81	0.001

LVD – LV end diastolic diameter , LVS - LV end systolic diameter , IVS – interventricular septum thickness in diastole PWT -LV posterior wall thickness in diastole, LA- left atrium diameter , RV basal – RV end diastolic diameter at base, RV mid – RV end diastolic diameter at mid cavity level , RV base to apex length, RVOT above AV - end diastolic diameter of right ventricular outflow tract above aortic valve, RVOT above PV- end diastolic diameter of right ventricular outflow tract above pulmonary valve, RVWT-right ventricular free wall thickness in diastole, PA - pulmonary artery diameter , RA right atrial diameter.

Echocardiographic functional parameters assessing left and right ventricular function in both the study groups are shown in Table 4. Left ventricular end diastolic volume, left ventricular end systolic volume, LV stroke volume and LV ejection fraction were not significantly different in the two groups. The mitral inflow velocities ratio (E/A) were significantly lower in COPD patients and deceleration time of E (DT), the isovolumetric relaxation time (IVRT) was significantly longer in relation to control group. The analysis of right ventricular systolic function parameters (RVED, RVSV, EF %)) was significantly different between the two study groups.

A total of 62 patients were recruited in our study and out of them, the number of patients with mild, moderate, severe, and very severe COPD were 19/62 = 30.7%, 25/62 = 40.3 %, 14/62 = 22.5%, and 4/62 = 6.5%, respectively [Table 6].

Tricuspid regurgitation (TR) was observed in 29 patients (29/62 = 46.8%). Mean PASP for the entire group in which TR could be measured was 52.03 mmHg. PH defined as sPAP> 30 mmHg was observed in 24patients (24/62 = 38.7% of the total study population). Out of those 24 patients with pulmonary hypertension, 11 patients were in mild PH (45.8%) 10 were in moderate PH (41.7%) and 3 were in severe PH (12.5%).

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Table 4: Echocardiographic parameters assessing left and right ventricular functions

Variable	COPD group n=62	Control group n=20	P value
LVDV(ml)	51.1±14.9	51.9±13.6	0.9
LVSV(ml)	20.5±8.57	19.9±8.05	0.8
SV(ml)	30.6±11.6	31.1±10.9	0.7
LVEF%	60.4±9.0	61.2±9.6	0.2
E peak (cm/sec)	0.71±0.24	0.1.12±0.18	0.0001
A peak(cm/sec)	0.97±0.34	0.87±0.39	0.01
Mitral E/A	0.73±0.21	1.24±0.28	0.0001
DT(ms)	238.9±54.9	216.9±41.2	0.001
IVRT(ms)	112.5±15.4	96.3±12.3	0.001
RVDV(ml)	51.4±18.17	35.4±6.3	0.0001
RVSV(ml)	36.9±16.9	15.2±4.6	0.0001
RVEF%	41.3±8.4	63.4±6.8	0.0001

LVDV - LV end diastolic volume , LVSV –LV end systolic volume , SV- stroke volume ,LVEF-LV ejection fraction , E peak- peak velocity of early diastolic filling , A- late filling with atrial contraction , E/A ratio- mitral inflow velocities ratio, DT- deceleration time of the E, IVRT - isovolumetric relaxation time , RVDV- RV end diastolic volume , RVSV – RV end systolic volume, RVEF- RV ejection fraction

Comparative study of various stages of severity of COPD reveals that as severity of COPD increases the prevalence of cardiac dysfunction increases, so more severe COPD is associated with more prevalent and more severe cardiac manifestations (Table 5).

Table 5: Echocardiographic parameters according to severity of COPD

Variable	Mild	Moderate	Severe	Very severe
FEV1of Predicted (%)	>80%	50-80%	30-50%	<30%
No of patients (%)	19 (30.7)	25 (40.3)	14 (22.5)	4 (6.5)
PH(>30mm hg) no (%)	1 (5.2)	8 (32)	11 (78.5)	4 (100)
Cor pulmonale no (%)	1 (5.2)	9 (36)	12 ((85.7)	4 (100)
RV dysfunction no (%)	0 (0)	2 (8)	8 (57.1)	3 (75)
LV systolic dysfunction no (%)	0 (0)	1 (4)	0 (0)	1 (25)
LV diastolic dysfunction no (%)	8 (12.9)	18 (72)	11 (78.5)	4 (100)

PH – pulmonary hypertension

DISCUSSION

COPD is associated with significant extra-pulmonary effects among which cardiac complications are most common. The cardiac manifestations of COPD are numerous. Impairment of RV function and alteration of pulmonary blood vessels are well known to complicate the clinical course of COPD and correlate inversely with survival. Due to remodelling of blood vessels, vasoconstriction and increase in blood viscosity there is a significant increase in pulmonary vascular resistance as a consequence of which pulmonary hypertension develops. Remodelling (intimal thickening and medial hypertrophy) in the smaller branches of the pulmonary arteries occurs due to hypoxemia and chronic ventilatory insufficiency. Pulmonary vasoconstriction occurs due to decrease in intrinsic pulmonary vasodilator substances (such as PGI_2 synthase, eNOS (endothelial nitric oxide synthase), and increase in vasoconstrictor substance ET1 (endothelin1). Pulmonary hypertension (PH) increases right ventricular after load resulting in right ventricle hypertrophy and dilation which eventually leads to right heart failure.

Pulmonary hypertension in the course of COPD is usually of a mild or moderate grade as confirmed by many studies [14, 15]. Although the true prevalence of PH in COPD is unknown, an elevation of pulmonary arterial pressure is reported to occur in 20%–90% of patients when measured by right heart catheterization [16-18]. Many studies showed that the level of PH has a prognostic value in COPD patients. In one of these studies, the 5-year survival rates were 50% in patients with mild PH (20–30 mmHg), 30% in those with moderate-to-severe PH (30–50 mmHg), and 0% in the small group of patients with very severe PH (>50 mmHg).

The present study reveals 38.7 % patients of various severity of COPD have findings of pulmonary hypertension that is similar to the prevalence of previous studies. In our study the frequencies of PH in mild, moderate, severe, and very severe COPD were 5.2 %, 32%, 78.5%, and 100%, respectively. In one study it was found to be 25%, 43%, and 68% in mild, moderate, and severe COPD, respectively [19]. In our

study it is also observed that the incidence of PH is directly proportional to severity of disease. In previous studies the frequency of severe PH in COPD varied from about 1%–3% [20, 21], but in our study it was (4 /62) 6.4%.

Cor pulmonale was present in 41.9 % of patients in our study. Cor pulmonale was found in 40% patients with COPD in one autopsy study [22]. In our study the frequencies of cor pulmonale in mild, moderate, severe, and very severe COPD were 5.2 %, 36%, 85.7%, and 100%, respectively. Approximately 25% patients with COPD eventually develop cor pulmonale and approximately 85% patients with cor pulmonale have COPD [23].

The influence of the right ventricular volume or pressure overload on the left ventricular function is known as the reverse Bernheim phenomenon, and is associated with the existence of a common interventricular septum, and the common pericardium cavities of the heart [24]LV ejection fraction in COPD patients, was in the normal range and did not differ significantly from control group. Similar results were obtained by other investigators [25,26]. In the absence of conditions primarily leading to left ventricular systolic function impairment the derangement of systolic function in the course of COPD is rarely found, usually in severe pulmonary hypertension, in patients with right ventricular dysfunction [27]. With normal ejection fraction, some investigators, however, suggest the presence of subclinical systolic dysfunction in the COPD patients [28]. Some studies indicate that LV function remains normal in persons with COPD, whereas others suggest that LV dysfunction may be present [29,30]. In the present study, left ventricular systolic dysfunction (LVSD) was present in 3.2% patients, in previous studies it was present in 4%–32% patients of COPD[31,32]. Abnormal LV systolic performance in COPD patients may be due to hypoxemia and acidosis; concurrent coronary artery disease; ventricular interdependence which would in turn increase LV end-diastolic pressure, decreased venous return, and diminished LV stroke volume and cardiac output (CO) and large swings in intrathoracic pressure [33].

In the case of right ventricular long-standing pressure overload the dominant role is played by the interventricular septum shift into the left ventricular cavity and this may result in the limitation of left ventricular cavity dimensions, its contractility and compliance and consequently in the rise of the left ventricular diastolic pressure . The relation between right ventricular pressure and left ventricular diastolic dysfunction in a large group of cor pulmonale patients of different etiology (including COPD patients), was confirmed by Mustapha et al. [34]. The development of relaxation diastolic dysfunction is most probable in patients with severe pulmonary hypertension. LVDD was also seen in COPD patients with normal pulmonary arterial pressure and it increased with right ventricular after load [35]. In our study LVDD was present in 66.1% of patients, out of which 24 patients had PH and 17 did not have PH. This may be due to chronic hypoxemia leading to abnormalities of myocardial relaxation, lung hyperinflation, and distension leading to increased stiffness of the parietal pleura and thus of myocardium, and also due to ventricular interdependence.

CONCLUSION

To conclude, the present study shows high prevalence of pulmonary hypertension, cor pulmonale, right ventricular systolic dysfunction and left ventricular diastolic dysfunction in COPD patients, and severity increases with level of severity of COPD. Impairment of left ventricular systolic function was rarely found in COPD patients. We suggest echocardiographic screening of all COPD patients so that early identification, close monitoring and intense treatment may improve prognosis of COPD patients.

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