Original Article

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Assessment of Diastolic Dysfunction Parameters and Cardiac Chamber Size in Smokers with COPD: A Case Control Study

Internal Medicine Section

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a critical health care burden across the globe. Pulmonary Hypertension (PH) is a widespread feature of advanced COPD and is estimated to affect 20% of individuals with advanced COPD.

Aim: To compare the variables of cardiac function, chamber size and diastolic parameters across various stages of COPD.

Materials and Methods: A prospective case control study was conducted among 50 subjects and 50 controls (convenient sampling) with COPD over a period of two years in kasturba Medical college, Manipal (July 2012-July 2014). Chronic smokers who met the criteria for COPD according to GOLD criteria were included in the study. All patients underwent Pulmonary Function Test (PFT) using spirometer.

Results: Twenty seven out of 50 studied patients (54%) had Pulmonary Artery Hypertension (PAH). Nineteen patients had mild PAH (38%). Dimension of cardiac chamber across various stages of COPD were found to have a significant decrease in Left Atrial (LA) area. Our study found an increase in Isovolumic Relaxation Time (IVRT), Pulmonary Artery Pressure (PAP) and TEI index (myocardial performance index) across stages of COPD however it was not statistically significant.

Conclusion: Majority of the patients with COPD had PH, with increasing frequency of PAH across the GOLD stages. A decrease in cardiac chamber size was demonstrated with increasing severity of COPD.

Keywords: Convenient sampling, Obstructive airway disease, Pulmonary hypertension

INTRODUCTION

Chronic obstructive pulmonary disease is a critical health care burden across the globe. The disease progression is manifested by progressive airflow limitation, hyperinflation and air trapping, hypoxaemia, hypercapnea, and elevations in pulmonary vascular pressures. Clinically, people with COPD develop shortness of breath, cough, sputum production and disease exacerbations that impair quality of life. Survival correlates negatively with pulmonary arterial pressure and pulmonary vascular resistance and individuals with COPD and PAH have increased morbidity and threat for hospitalisations for acute COPD exacerbations [1].

Pulmonary hypertension is a widespread feature of advanced COPD and is estimated to affect 20% of individuals with advanced COPD [2]. Among COPD patients, Cardiovascular Disease (CVD) is responsible for roughly half of all hospitalisations and 20% of all fatality [3]. The population based studies have proposed that paying little heed to smoking status, age or sex, a COPD determination builds the danger of cardiovascular grimness and mortality by roughly two folds [4]. Left Ventricular Diastolic Dysfunction (LVDD) is an incessant condition in COPD patients. Inflammation is thought to be one of the systemic manifestation of COPD and gives an option of speculation to clarify the relationship between airflow limitation and cardiovascular hazard [5-7]. Given the prognostic ramifications of CVD in COPD, its identification could serve as a manual for proper treatment and inevitably enhance survival.

Measurements of the left and right ventricle are smaller in patients with serious emphysema. This perception is accompanied by a decreased intrathoracic blood volume and disabled left ventricular filling process. Diminished preload brought on by hyperinflated lungs may be in charge of these cardiovascular variations from the normal, in the extremely serious phase of the disease [8].

However, a relationship of abnormal lung function, particularly hyperinflation, with decreasing heart size and left ventricular filling process is not well established. We conducted this study to compare the variables of cardiac function, chamber size and diastolic parameters across various stages of COPD.

MATERIALS AND METHODS

Study Population

A case control study was conducted among 50 subjects with COPD and 50 controls over a period of two years in Kasturba Medical College, Manipal, Karnataka, India (July 2012 to July 2014).

Age matched nonsmokers without any premorbid condition were taken as controls.

Exclusion Criteria

Subjects were excluded if they had any of the following conditions, such as treatment for or evidence of arterial hypertension on clinical examination, diabetes mellitus, valvular heart disease, history of significant coronary artery disease, bronchogenic carcinoma, significant Interstitial lung disease, atrial tachyarrhythmias and/or signs of left ventricular hypertrophy on a standard ECG, bronchial asthma, nonsmokers with COPD and patients with systolic dysfunction (ejection fraction <50%) were also excluded.

Inclusion Criteria

Chronic smokers who met the criteria for COPD according to GOLD criteria were included in the study. Number of cigarettes was expressed as pack-year. All individuals underwent history taking, physical examination, ECG, chest radiograph, PFT and echocardiography. The study protocol was approved by the Ethics

Committee of the Institution and informed consent was obtained prior to study entry.

Pulmonary Function Test

All patients underwent PFT using a spirometer. Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV1) and FEV1/FVC were measured. Post-bronchodilator spirometry (15 minutes after 400 µg of salbutamol) was done in all patients to rule out reversibility and exclude patients with bronchial asthma.

Echocardiography

Echocardiography (Echo) was performed in all patients according to the same protocol with the use of GE Medical System Vivid7 ultrasound machine equipped with 1.5–4 MHz sector transducer probe. All individuals were studied in left lateral recumbent position. Images were obtained from the parasternal views (long axis and short axis), the apical four chamber view, and the subcostal view. All measurements were performed at end expiration.

Left atrium area, right atrium area, left ventricular end-diastolic diameter, and right ventricular diameter were measured in apical four chambered view [9].

Diastolic function of the left ventricle was assessed using IVRT, deceleration time of the early transmitral flow and ratio of the peak velocity of the early E-wave to atrial A-wave. According to a simplified approach, diastole was divided into relaxation represented in part by IVRT and diastolic filling, represented in part by deceleration time of the early transmitral flow and ratio of the peak velocity of the early E-wave to atrial A-wave [10]. Also, the Early diastole (E') and Atrium systole (A') mitral valve annular velocity were measured at the lateral wall of the left ventricle by pulsed wave tissue Doppler and similarly, the E/E' ratio was derived.

Parameters obtained through long axis parasternal approach in M-mode projection were analysed: end-diastolic Right Ventricular Diameter (RVD), Left Ventricular End-Diastolic (LVEDD), Interventricular Septum Thickness (IVS), Posterior Wall (PW), Ejection Fraction (EF) and Fractional Shortening (FS).

The E/E' ratio has been identified as the best parameter for diagnosis when compared to other Doppler measures. Hence septal E/E' ratio was used for assessing diastolic dysfunction [11].

The subjects were classified in following groups:

1. Normal LV function-when E/E' ratio <8 cm/s.
2. Diastolic dysfunction-when E/E' ratio >8 cm/s.

The Right Ventricular Systolic Pressure (RVSP) was derived from the velocity of tricuspid regurgitation using the modified Bernoullie equation. The calculated RVSP correlated with mean PAP excluding a significant pulmonary stenosis [12].

Severity of COPD was graded on the basis of PAP [12].

Normal- <30 mmHg

Mild- 30-40 mmHg

Moderate– 40-60 mmHg

Severe- >60 mmHg

STATISTICAL ANALYSIS

The results obtained in the COPD patients group and in the control group were compared by independent sample t-test. A linear regression analysis with the 95% confidence interval and derived regression ratio was employed to investigate the relation between obtained data. Analysis of variance (ANOVA) was performed to analyse the differences of cardiac chamber sizes and heart function across the GOLD stages. A p-value of 0.05 was considered to be statistically significant. Data analysis was performed with the statistical software SPSS version 16.0.

RESULTS

Maximum number of COPD patients (20 out of 50) in the study were in the age group of 60-69 years with mean age 61.14±10.33 years. PAH was present in 54% of patients across various stages of COPD in our study. Majority of the patients belonged to GOLD stage 4. PAH was also more prevalent in stage 4 COPD patients [Table/Fig-1].

Age (years)	No. of patients (%)
<50	7 (14)
50-59	15 (30)
60-69	20 (40)
>70	8 (16)
Baseline characteristics	
GOLD Stage 1,2	10 (20)
GOLD Stage 3	19 (38)
GOLD Stage 4	21 (42)
Pulmonary Artery Hypertension	
No PAH	23 (46)
Mild PAH	19 (38)
Moderate PAH	7 (14)
Severe PAH	1 (2)
GOLD Staging and PAH	
GOLD Stage 1,2	5 (10)
GOLD Stage 3	8 (16)
GOLD Stage 4	14 (28)

[Table/Fig-1]: Demographic and baseline characteristics.
PAH-Pulmonary artery hypertension

Left atrium area in cases and control group were 12.2±2.90 cm^2 and 11.2±1.98 cm^2 respectively. A statistically significant difference in LA area (p=0.035) was found between two groups [Table/Fig-2]. We found a statistically significant difference in mean RV diameter among cases and controls (p<0.001) (Higher in cases compared to controls).

We found a statistically significant difference between mean Mitral E and Mitral A among cases and controls [Table/Fig-3] (p=0.01 and p<0.001) respectively.

Diastolic dysfunction parameters between studied groups are mentioned in [Table/Fig-4]. There was no significant difference between Mitral E/A among studied groups (p=0.183). However, we found a statistically significant difference between Septal E/E' and

Chamber size	Cases	Controls	p-value
RA area (cm^2)	11.3 ±2.69	10.6±2.28	0.133
LA area (cm^2)	12.2±2.90	11.2±1.98	0.035
LV diameter (cm)	4.45±0.55	4.61±0.50	0.133
RV diameter (cm)	2.95±0.49	2.48±0.31	<0.001

[Table/Fig-2]: Chamber size in cases and controls.
*The dimension of heart cavities between studied groups were compared using independent sample t-test.
RA–Right atrium, LA–Left atrium, LV–Left ventricle, RV–Right ventricle

Tissue doppler	Cases	Controls	p-value
Lateral E	0.1±0.03	0.12±0.02	0.01
Lateral A	0.1±0.02	0.1±0.03	0.87
Mitral E	0.86±0.33	0.73±0.14	0.01
Mitral A	0.82±0.21	0.63±0.17	<0.001

[Table/Fig-3]: Tissue doppler indices.
Diastolic dysfunction parameters between studied groups were compared using independent sample t-test (Lateral E–Velocity along lateral wall of left ventricle during early diastole
Lateral A–Velocity along lateral wall of left ventricle during atrial systole
Mitral E–Mitral annular velocity during early diastole
Mitral A–Mitral annular velocity during atrial systole)

Lateral E/E' between cases and controls (p=0.003 and p<0.001 respectively) (Higher in cases compared to controls).

We found a significant decrease in LA area across the stages of COPD (p=0.006). There was no significant difference in LV diameter, RV diameter and RA area across stages of COPD [Table/Fig-5]. Tukey's HSD post-hoc analysis showed significant difference of LA area between GOLD 1,2 vs GOLD 3 (p=0.04) and GOLD 1,2 vs GOLD 4 (p=0.004), however there was no significant difference between GOLD 3 and GOLD 4.

We found an increase in IVRT, PAP and TEI index (myocardial performance index) across stages of COPD however, it was not statistically significant [Table/Fig-6].

Tissue doppler	Cases	Controls	p-value
Mitral E/A	1.11±0.48	1.23±0.39	0.183
Septal E/E'	10.2±4.19	8.22±2.27	0.003
Lateral E/E'	8.78±4.27	6.24±2.09	<0.001

[Table/Fig-4]: Diastolic dysfunction parameters.
Diastolic dysfunction parameters between studied groups were compared using independent sample t-test
Mitral E/A-Ratio of the peak velocity of the early mitral annular E-wave to mitral annular atrial A-wave
Septal E/E'-Ratio of the peak velocity of the early mitral annular E-wave to early diastolic velocity at the septum
Lateral E/E'-Ratio of the peak velocity of the early mitral annular E-wave to early diastolic velocity at the lateral wall of left ventricle)

	GOLD 1,2	GOLD 3	GOLD 4	p-value
LV diameter (cm)	4.62±0.46	4.48±0.62	4.34±0.51	0.413
RV diameter (cm)	2.79±0.31	3.04±0.34	2.96±0.64	0.416
LA area (cm^2)	14.69±2.25	12.11±2.81	11.26±2.69	0.006
RA area (cm^2)	12.87±2.48	10.80±1.83	11.21±3.24	0.134

[Table/Fig-5]: Chamber size and severity of COPD.
Data are presented as mean±SD. p-values were tested by analysis of variance for linear trend
LV–Left ventricle, RV–Right ventricle, LA–Left atrium, RA–Right atrium

	GOLD 1,2	GOLD 3	GOLD 4	p-value
IVS	0.990±0.19	0.994±0.12	1.00±0.12	0.981
IVRT	77.30±16.87	77.95±17.92	83.57±21.86	0.581
PAP	30.00±6.28	31.68±12.39	35.14±14.05	0.491
TEI	0.50±0.17	0.51±0.14	0.53±0.10	0.681

[Table/Fig-6]: Cardiac function parameters and severity COPD.
Data are presented as mean±SD. p-values were tested by analysis of variance for linear trend
IVS–Inter ventricular septum, IVRT-Isovolumic relaxation time, PAP-Pulmonary artery pressure, TEI Index-Myocardial Performance Index

DISCUSSION

The main finding of the present study was the evidence obtained for left ventricular diastolic dysfunction in patients with COPD. A total of 50 patients diagnosed with COPD were enrolled in the study. We performed a case control study between the cases and age matched controls to compare cardiac chamber size and diastolic dysfunction parameters.

COPD and Pulmonary Artery Hypertension

Pulmonary hypertension is a frequent complication of COPD associated with frequent exacerbation and decreased survival. PH is usually exaggerated by exercise, sleep and exacerbation. Pulmonary vascular remodelling leads to increase in PAP which in turn results from combined effects of hypoxia, inflammation and loss of capillaries in severe emphysema [13].

Pulmonary artery hypertension was present in 54% of patients across various stages of COPD in our study. In a study by Gupta NK et al., the frequencies of PH in mild, moderate, severe, and very severe COPD were 16.67%, 54.55%, 60.00%, and 83.33%, respectively [14]. In another study by Higham MA et al it was found to be 25%, 43%, and 68% in mild, moderate, and severe COPD, respectively [15].

Pulmonary hypertension has a prognostic role in patients with COPD. Five year survival rates varies from 50% in patients with mild PH (20–30 mmHg) to 30% in those with moderate-to-severe PH (30–50 mmHg) [16].

Chamber Size

Statistically significant difference in mean RV diameter was found in patients with COPD as compared to age matched controls (Higher in cases compared to controls). Similar results were found in study performed by Boussuges A et al., and Suchon E et al., [12,17]. PH overloads the RV, enlarges right heart chambers and ultimately causes right ventricular failure.

To our knowledge, this is the only study which used LA area and RA area to assess chamber size in cases and controls. We found a significant higher LA area in cases as compared to controls. This may be due to abnormal diastolic function in cases as compared to controls. It is known that left atrial dilatation correlates positively with LV filling pressure which is increased in diastolic dysfunction [18].

Tissue Doppler Indices

In the current study, we used various tissue Doppler indices to compare diastolic dysfunction between cases and controls.

Boussuges A et al., Suchon E et al., and Funk GC et al., showed a lower mitral E/A in COPD patients as compared to control group [12,17,19]. However, in present study, we found higher mitral E/A among cases than controls. A possible explanation could be due to higher mitral E in cases than controls. As greater proportion of cases had moderate diastolic dysfunction, mitral E was higher in them as compared to controls possibly due to pseudonormalisation.

Age is one of the most cited factors that usually modify the LV filling profile. In young subjects, LV elastic recoil is vigorous and myocardial relaxation is swift, so most of the LV filling is completed during early diastole (E wave) with only a small contribution of filling during the atrial contraction (A wave) [20].

With age, early filling decreases and the contribution of the atrial contraction increases. Inverse E/A ratio is normally observed in subjects older than 60 yr of age [20]. However, in the present study, interference by age is less likely as subjects and controls were age matched.

Multiple factors affect the LV filling profile in patients with COPD. The first and most important factor is the significantly increased heart rate in the COPD group. Tachycardia shortens the diastolic filling period and so atrial contraction occurs before the early filling is completed. Hence, the transmitral A peak velocity will be higher than expected. This tachycardia may be due to multiple reasons like hypoxia or medications in patients with COPD [20].

Mitral E/A is not a good indicator to measure diastolic dysfunction in patients with COPD as it is affected by various factors like heart rate and rhythm, PR interval, cardiac output, mitral annular size, and LA function [11].

In view of the limitations of Mitral E/A, we used other tissue Doppler indices like septal E/E' and lateral E/E' to compare diastolic dysfunction between cases and controls. We found a statistically significant difference in septal E/E' and lateral E/E' between the two groups (Higher in cases as compared to controls). To our knowledge, none of the other studies have measured these Doppler indices to compare diastolic dysfunction between the two groups.

Chamber Size and Severity of COPD

Hyperinflation is a major lung function abnormality in patients with COPD, which is related to exercise limitations and mortality. Hyperinflation of the lungs leads to diaphragm lowering and diaphragm dysfunction. The role of hyperinflation for heart size and heart dysfunction has been less studied [8].

Watz H et al., studied the cardiac chamber sizes and cardiac parameters across GOLD stages [8]. Though, cardiac chamber sizes

and peak velocity of the early E-wave to atrial A-wave decreased across GOLD stages, other variables like deceleration time of the early transmitral flow and Tei-index increased across GOLD stages while IVRT remained constant across GOLD stages.

However in the present study, we found a significant difference only in LA area across GOLD stages (LA area decreases across GOLD stages) (p=0.006). We did not find a significant increase in IVRT, Tei-index and PAP. A possible explanation could be a smaller sample size. As few cases were found to have corpulmonale, RV diameter and RA area might have been influenced by it.

LIMITATION

Sample size was smaller and performing Echo is always is difficult in patients with COPD because of the limited acoustic window; therefore, some bias cannot be excluded.

CONCLUSION

Majority of the patients with COPD had PH with increasing frequency of PAH across the GOLD stages. There was a significant diastolic dysfunction in patients with COPD as compared to age matched controls. However, diastolic dysfunction was found even in cases with normal PAP. Newer tissue Doppler indices like septal E/E' and lateral E/E' are better markers to compare diastolic dysfunction between cases and controls. A decrease in cardiac chamber size was demonstrated with increasing severity of COPD.

ABBREVIATIONS

COPD-Chronic Obstructive Pulmonary Disease; PH-Pulmonary Hypertension; PFT-Pulmonary Function Test; PAH-Pulmonary Artery Hypertension; LA-Left Atrial; IVRT-Isovolumic Relaxation Time; PAP-Pulmonary Artery Pressure; CVD-Cardiovascular Disease; LVDD-Left Ventricular Diastolic Dysfunction; Echo-Echocardiography; FVC-Forced Vital Capacity; FEV1-Forced Expiratory Volume; E'-Early diastole; A'-Atrium systole; RVSP-Right Ventricular Systolic Pressure; RA–Right Atrium; LA–Left Atrium; LV–Left Ventricle; RV–Right Ventricle; IVS-Interventricular Septum Thickness; TEI Index-Myocardial Performance Index.

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