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CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS AND ITS CLINICAL EFFECTS ON THE LEFT VENTRICULAR FUNCTION

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ABSTRACT

Background: In chronic obstructive pulmonary disease (COPD) patients, left ventricular (LV) systolic dysfunction is rare. However, abnormal LV diastolic dysfunction has been frequently reported in patients with COPD. **Objectives:** To evaluate the prevalence of left ventricular systolic or diastolic dysfunction in patients with COPD. **Materials and Methods:** A total of 102 patients diagnosed with COPD as per GOLD guidelines were enrolled. These patients underwent physical examination and standard two-dimensional echocardiographic views, and peak flow velocity of early diastolic filling (Emax), peak flow velocity of late atrial filling (Amax) and early flow velocity peak/late flow velocity peak (E/A) ratio were measured according to the criteria's of American Society of Echocardiographers. **Results:** Of the 102 COPD patients, the maximal atrial filling velocity (A-Max) was increased and early filling velocity (E-Max) was decreased in 76 patients (74.5%) ($p < 0.001$). The early flow velocity peak/late flow velocity peak (E/A) ratio was also markedly decreased in these 76 patients ($p < 0.001$) indicating left ventricular dysfunction. The atrial contribution to total left diastolic filling was increased in patients with COPD. This was also observed in COPD patients with normal PAP ($p < 0.001$). Grade IV

COPD (p-0.000), duration of illness (p<0.001), smoking >10 pack years (p<0.001) were the risk factors which were associated with development of LV diastolic dysfunction in COPD patients. **Conclusion:** In the present study, the prevalence of left ventricular diastolic dysfunction was 74.5%. As the severity of COPD increased, the risk of left ventricular diastolic dysfunction increased. The screening of severe COPD patients for left ventricular function will improve the outcome in these cases.

KEYWORDS: COPD, left ventricular dysfunction, pulmonary arterial pressure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a syndrome of progressive airflow limitation caused by the abnormal inflammatory reaction of the airway and lung parenchyma. It is now considered a systemic disease with widespread extra-pulmonary manifestations.[1] It remains a major public health problem and is projected to be rank fifth, in 2020 in burden of disease world wide.[2] In India it is estimated that there are around 1.49 crore cases of COPD and the prevalence rates of COPD in males varies from 2.12% to 9.4%, and these are projected to increase by nearly 50% by the year 2016.[3]

Abnormal patterns of left ventricular diastolic filling have been reported in patients with increased right ventricular pressure and/or volume load, suggesting that left ventricular filling dynamics may be influenced by right ventricular loading conditions.[4] Several studies[5,6] have demonstrate decreased right ventricular volumes, reflecting right ventricular after load, in patients with COPD and mild pulmonary artery hypertension. In a recent study, Dario-Vizza and colleagues assessed the frequency of systolic dysfunction to be less than 5%.[5] Chronic heart failure is also common amongst COPD patients and in a recent study over 20% of patients were found to have undiagnosed left ventricular failure by magnetic resonance imaging.[6] Derangement of the left ventricular (LV) function in such patients, in the absence of other disorders affecting the LV, has not been clearly established.[7] Clinical studies have suggested that LV hypertrophy may occur in patients with chronic cor pulmonale by means of biochemical and anatomic changes, including a decreased concentration of norepinephrine, an abnormal histochemical appearance of the adrenergic nerve fibers, a depressed myofibrillar adenosine triphosphatase activity, and an increased amount of collagen fibers.[8] Hence the present study was done to determine the prevalence of left ventricular diastolic dysfunction in COPD patients.

MATERIALS AND METHODS

The present study was conducted in the Department of Pulmonary Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum in COPD patients during the period of January 2012 – December 2013. A total of 102 cases of COPD, diagnosed as per GOPD guidelines[2] were included in the analysis. The diagnosis of COPD was done based on clinical history and pulmonary function testing and staging done as per GOLD Criteria. Patients with valvular heart disease, angina pectoris, ischaemic heart disease, cardiomyopathy, rheumatic heart disease were excluded.

Procedure: The selected patients were briefed about the study and written informed consent was obtained. Baseline and demographic characteristics were collected for all the patients. The patients were subjected to pulmonary function tests and ECHO to stage the severity of COPD and the presence or absence of diastolic dysfunction respectively. Pulmonary function testing was done using RMS Helios 702 spirometer (Recorders and Medicare Systems Pvt. Ltd MEDSPIROR, India). The following values were obtained from the test: FEV_1, FVC, FEV_1/FVC ratio, SVC and MVV. FEV_1 and FVC and FEV_1/FVC ratio were the main parameters used to stage the COPD according to GOLD guidelines.[2] Post bronchodilator spirometry was performed in all the patients to exclude the diagnosis of bronchial asthma. Staging of COPD was done according to GOLD guidelines. Standard two-dimensional echocardiographic views were used to obtain standard parasternal, apical, and subcostal views in order to measure systolic and diastolic left ventricular dimensions and for calculations of left ventricular fractional shortening. Measurements of interventricular septum thickness were also done. Measurements were made according to the American Society of Echocardiographers guidelines.

Diastolic Dysfunction: The heart failure with preserved ejection fraction (Diastolic dysfunction) is defined on the basis of clinical finding congestive heart failure with the echocardiography findings of preserved left ventricular ejection fraction and valvular abnormalities. Diastolic flow from the left atrium and left ventricle across the mitral valve has two components: E wave, early diastolic filling and A wave, atrial contraction. In late diastole, E wave velocity is influenced by both the rate of early diastolic relaxation and the left atrial pressure. An alteration in the pattern of E wave velocity reflects the degree of left ventricular diastolic dysfunction and prognosis.

Tissue Doppler imaging directly measures the velocity of change in myocardial length as an index of left ventricular relaxation. On echocardiography, the peak velocity of blood flow across the mitral valve during early diastolic filling corresponds to the E wave. Similarly, atrial contraction corresponds to the A wave. From these findings, the E/A ratio is calculated. Under normal conditions, E is greater than A and the E/A ratio is approximately 1.5m/s. In early diastolic dysfunction, relaxation is impaired and, with vigorous atrial contraction, the E/A ratio decrease to less than 0.75 m/s. As the disease progresses, left ventricular compliance is reduced, which increases left atrial pressure and, in turn, increases early left ventricular filling despite impaired relaxation. This paradoxical normalization of the E/A ratio is called pseudonormalization. In patients with severe diastolic dysfunction, left ventricular filling occurs primarily in early diastole, creating an E/A ratio greater than 2.0 m/s.

Grading of Diastolic Dysfunction (or Diastolic Filling Pattern)

Grade 1 (mild dysfunction): Mitral E velocity is decreased and A velocity is increased, producing an E/A ratio of less than 0.75 m/s, with prolonged DT.
Grade 2 (moderate dysfunction): As diastolic function worsens, the mitral inflow pattern goes through a phase resembling a normal diastolic filling pattern, that is, an E/A ratio of 1 to 1.5 m/s and normal DT (160 to 240 milliseconds).

Grade 3 and Grade 4 (severe irreversible dysfunction): Restrictive filling with severe diastolic dysfunction is characterized by increased E velocity, decreased A velocity (markedly less than E) with an E/A ratio higher than 2 m/s, and shortened DT (<160 milliseconds) and IVRT (<70 milliseconds).

The study was approved by the ethical and research committee of Jawaharlal Nehru Medical college, Belgaum.

Statistical Analysis: This is a cross sectional study in which prevalence of left ventricular diastolic dysfunction in COPD was evaluated. Prevalence of left ventricular diastolic dysfunction in COPD was estimated by considering all the COPD patients attending the respiratory clinic. Left ventricular diastolic dysfunction was co-related with risk factors of COPD by one way analysis of variance (ANOVAs test).

RESULTS

A total of 102 patients with COPD were included in the study. Male: female ratio was 1.7:1 (Table 1). Nearly two-third patients had more than 5 years of COPD illness. Another two-third of the patients had either Stage III or Stage IV of the COPD disease. A total of 45.1% of the patients were smokers, and 60.8% had normal BMI.

In the present study, a total of 76 patients (74.5%) had left ventricular diastolic dysfunction, while rest 24 patients had normal left ventricular function. Among these 76 patients with diastolic dysfunction, 6 patients (5%) had associated systolic dysfunction and 70 patients (95%) had only diastolic dysfunction. A total of 29 patients (38.2%) in stage II and 32 patients (42.1%) in stage II COPD had diastolic dysfunction as assessed by ECHO (Table 2). None of the patients at stage I COPD had any diastolic dysfunction. A-Max was increased as compared to E-Max and thus, E/A Ratio was decreased when compared between the patients with and without diastolic dysfunction ($p<0.000$). Stage I and stage II COPD disease had less prevalence of left ventricular dysfunction. Also it is observed, that as the severity grade of COPD increased, the risk of left ventricular dysfunction had also increased (Table 3).

Comparative evaluation was done among patients in COPD with presence of increased pulmonary arterial hypertension (PAP) and with normal arterial pressure. It was observed that the maximal atrial filling velocity (A-Max) was increased and the early filling velocity (E-Max) was decreased in patients with COPD with increased PAP. The atrial contribution to total left diastolic filling was increased in patients with COPD with increased PAP. This was also observed in COPD patients with normal PAP ($p<0.000$) (Table 4).

Table 1. Baseline characteristics of the patients

Baseline characteristics	No	%
Sex distribution:		
Males	64	62.7
Females	38	37.3
Mean Age:		
Males (Years)	72 ± 5.2	
Females (Years)	68 ± 4.3	
Duration of illness:		
< 5 years	30	29.4
5 – 10 years	60	58.8
> 10 years	12	11.7
Stages of COPD:		
Stage I	4	3.9
Stage II	28	27.4

Stage III	32	38.2
Stage IV	31	30.9
BMI:		
Normal	62	60.8
Underweight	10	9.8
Overweight	22	21.6
Obese	8	7.8
Smoking status:		
Smokers	46	45.1
Non-smokers	56	54.9

Table 2. COPD stages and Left Ventricular Diastolic Dysfunction

COPD stage	DD Grade I No (%)	DD Grade II No (%)	DD Grade III No (%)	DD Grade IV No (%)	Total No (%)
Stage I	0	0	0	0	0
Stage II	10 (13.3)	7 (9.2)	0	0	15 (19.7)
Stage III	17 (22.3)	7 (9.2)	4 (5.2)	1 (1.3)	29 (38.2)
Stage IV	12 (15.4)	9 (11.8)	7 (9.2)	5 (6.5)	32 (42.1)
TOTAL	39 (51)	23 (30.2)	11 (14.4)	6 (7.8)	76 (100)

Table 3. Grades of Diastolic dysfunction in relation to COPD severity

	GRADE I	p value	GRADE II	p value	GRADE III	p value	GRADE IV	p value
E-MAX-N	0.48±0.16	0.000	0.57±0.18	0.001	0.67±0.12	0.001	0	0.000
E-MAX-DD	0		0.35±0.11		0.47±0.22		0.46±0.20	
A-MAX-N	0.64±0.08	0.000	0.45±0.13	0.001	0.45±0.12	0.001	0	0.000
A-MAX-DD	0		0.70±0.07		0.65±0.16		0.70±0.11	
E/A-N	0.83±0.35	0.000	1.35±0.55	0.001	1.57±0.07	0.001	0	0.000
E/A-DD	0		0.56±0.28		0.73±0.40		0.64±0.27	

Table 4: Diastolic dysfunction in patients with COPD patients and its Its relation to pulmonary arterial pressure (PAP)

	PAP With DD		PAP without DD		p value
	Mean	SD	Mean	SD	
RV FREE WALL	0.57	0.18	0.76	0.12	0.000
P A	2.23	0.40	2.67	0.16	0.000
A C T	32.2	13.9	47.2	7.2	0.001
I V S	89.4	24.6	73.8	28.4	0.003
PPG	1.2	0.41	1.5	0.24	0.001
RVEDD	22.7	6.0	26.4	6.9	0.000
RVESD	22.9	4.4	26.8	1.4	0.000
LVESD	40.1	8.0	32.8	0.84	0.001
LVEDD	27.02	8.1	19.2	1.90	0.001

Table 5: Prevalence of Left Ventricular dysfunction in COPD

Study	Patient group	Subjects	Cardiac Measurements	Prevalence of Systolic Dysfunction %	Prevalence of Diastolic Dysfunction %
Stele et al[14]	Severe COPD	120	ECHO	21	60
Berger et al[15]	COPD Suspected	27	ECHO	10	72
Mac Nee et al[16]	COPD patients with ambulation	36	ECHO	14	65
Zema et al[17]	Advanced COPD	37	ECHO	36	68
McCollough et al[18]	COPD with LV Dysfunction	417	ECHO	46	78
Present study	COPD Patients	102	ECHO	8	74

DISCUSSION

The main finding of the present study was the evidence obtained for left ventricular diastolic dysfunction in patients with COPD. A total of 102 patients were evaluated, and it was observed that 76 patients (74.5%) had diastolic dysfunction and 24 patients (25.5%) had normal left ventricular function. Among these 76 patients with diastolic dysfunction, 6 patients (5%) had also systolic dysfunction and 70 patients (95%) had only diastolic dysfunction. Dario-Vizza et al[5] also observed that the frequency of systolic dysfunction to be less than 5% in COPD cases. According to Gomez et al,[9] the frequency of abnormalities in LV relaxation has been suggested to be approximately 90% in patients with COPD. Malerba et al[10] has observed the incidence of left diastolic dysfunction in COPD to be 65%, while in another study, Steinberg et al,[11] has observed the incidence of diastolic dysfunction to be 78% in COPD patients. Kjaergaard[12] in a cross-sectional study has observed that the incidence of diastolic dysfunction increased more steeply with age in women and stated that there is an increased female predominance in diastolic dysfunction. Similarly, Steinberg et al[11] observed a higher occurrence of diastolic dysfunction among female population in their study. However, in our study there was an increased male predominance of diastolic dysfunction as compared to female patients; this may be due to the increased incidence of COPD in males due to smoking.[13]

The incidence of systolic dysfunction in COPD ranges from 8% to 46% and the diastolic dysfunction ranges from 54% to 92%. Table 5 summarizes the prevalence of left ventricular dysfunction in COPD in various studies. The varied difference in different study groups can be attributed to the methodological differences in the assessment of left ventricular dysfunction and also patient characteristics chosen for the study. In the present study, among the COPD patients diagnosed with diastolic dysfunction, 30 patients (40%) had associated pulmonary arterial hypertension (PAH) and 46 patients (70%) had normal pulmonary arterial pressure. In one prospective study by Funk et al,[19] it was observed that the maximal atrial filling velocity was increased and the early filling velocity was decreased in COPD patients with pulmonary arterial hypertension as compared to control subjects. The atrial contribution to total left diastolic filling was increased in patients with COPD. This was also observed in COPD patients with normal pulmonary arterial pressure, as ascertained using a right heart catheter. The atrial contribution to total left diastolic filling was further increased in COPD patients with PAP. This is in accordance with our study where in diastolic dysfunction was present in 46 patients (70%) with normal pulmonary arterial pressure. We also observed that there was an increase in the maximal atrial filling velocity (A-Max) and early filling velocity (E-Max) was decreased with an inverse E/A ratio.

Several factors might influence the left ventricular diastolic dysfunction in COPD patients. Patients with COPD experience chronic hypoxemia, which might result in abnormalities of myocardial relaxation as a consequence of myocyte hypoxia due to intracellular calcium transport disturbances,[20] and with advancing age the left ventricular relaxation decreases leading to increase in the isovolumetric time causing diastolic dysfunction.[21] This appeared to represent concentric remodeling, because relative wall thickness increased with age leading to diastolic dysfunction.[22] The cardiac fossa is a physiologic constraint at normal heart volumes. It acts to restrict ventricular expansion before pericardial restriction. The physiologically useful inter ventricular interdependence is thereby promoted. The effect of lung inflation in tensing the walls of the fossa may also sometimes embarrass both ventricles. Together with the raised intrathoracic pressure, it is responsible for the fall in left and right ventricular volumes and output during positive pressure ventilation.[23]

In the present study it was observed that an increased atrial contribution leading to total diastolic filling in patients with COPD indicates reduced E-max and a compensatory increase in late diastole at a time when septal geometry is less deranged. These concepts of left

diastolic dysfunction are based on the presence of pulmonary hypertension and/or hypoxemia in COPD patients. Boussuges et al[24] has observed similar results in moderate-to-severe COPD patients using combined analysis of pulmonary venous and mitral blood flow velocities. It was also observed that there was an impaired left ventricular filling and an increased contribution of atrial contraction to left ventricular filling despite normal systolic left ventricular function as compared with control subjects. Aldrich et al[25] has observed that positive end expiratory pressure (auto-PEEP) is common in patients with airways obstruction due to dynamic hyperinflation, and even without overt ventilatory failure, and its severity is generally in proportion to the severity of the hyperinflation and the airways obstruction, thus limiting the venous return leading to diastolic dysfunction in COPD patients. Yilmaz et al[26] has also observed that there is impairment in both LV systolic and diastolic functions in COPD patients, especially in patients with pulmonary hypertension. This impairment is independently associated with pulmonary arterial systolic pressure, RVMPI, and FEV_1.

Thus it is evident from the present study that the incidence of diastolic dysfunction is higher in cases of COPD patients, and maximal atrial filling velocity (A-Max) was increased and the early filling velocity (E-Max) was decreased in patients with COPD. The early flow velocity peak/late flow velocity peak (E/A) ratio was markedly decreased in these patients. The atrial contribution to total left diastolic filling was increased and this was also observed in COPD patients with normal PAP. COPD is now increasingly being recognized as an inflammatory condition of the lung, and, over the past decade, it has been recognized for its systemic inflammation and having extra-pulmonary manifestations.

Antonison et al,[27] reported the incidence of diastolic dysfunction in cases of COPD to be 45%. Similarly, Zvezidin et al[28] reported that the incidence of diastolic dysfunction in COPD to be 38% across all severity grades. In the present study, we divided the incidence of diastolic dysfunction according to the severity of COPD and observed that the maximum incidence was in COPD Stage IV disease (31%) as compared to other stages. Systemic inflammation may provide the biological link between the two, i.e., a common tumour necrosis factor-alpha (TNF-α) mediated pathogenesis underlying these diseases. Other common mediators may be of importance, such as IL -6 and IL-18. Systemic inflammation is now believed to be contributory factor to the clinical manifestations and natural history of COPD, and is an essential component of the COPD disease process and in diastolic dysfunction.[28,29] Caram et al[30] studied the role of obesity in COPD patients with diastolic

dysfunction, and reported that the patients who were overweight had higher incidence of diastolic dysfunction (61.9%), while in another study, the incidence of diastolic dysfunction was 58% in overweight patients with COPD. This may be due to increased body adiposity in obese individuals, changes in cardiac metabolism occur leading to myocardial fatty infiltration, inflammation and cardiac toxicity, with the end result being diastolic dysfunction.[32]

Thus, it can be concluded that in an ideal set up, all patients with COPD should be screened for diastolic dysfunction using echocardiography, which is considered for the early diagnosis and proper therapy of this condition can be advised at the earliest. This will help in improving the quality of life in these patients and prolonging the survival.

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