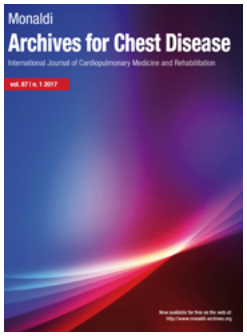

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Assessment of left ventricular function in subjects with chronic obstructive pulmonary disease

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Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article. The manuscript does not contain any individual person's data in any form.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

Abstract

Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death, posing a significant public health challenge. Heart failure is an important milestone in the natural history of this disease's ever-decreasing course. Cor pulmonale alone is sometimes insufficient to explain the scenario, as many heart failures are refractory even after standard treatment. A possible explanation is involvement of the left ventricle (LV). However, there is currently no consensus on a therapeutic approach to LV dysfunction in COPD. Some previous studies were conducted on COPD patients regardless of the presence or absence of other factors influencing LV function. This study attempted to rule out all known confounding factors/co-morbidities that influence LV function. We discovered that LV diastolic dysfunction was common in subjects at all stages of COPD. We believe that all COPD patients, regardless of stage, should have screening echocardiography.

Key words: COPD, LV diastolic dysfunction, LV systolic dysfunction, echocardiography, E/A.

Introduction

Chronic obstructive pulmonary disease (COPD), though preventable and treatable, is currently being ranked the third leading cause of death worldwide [1]. Globally, the reported prevalent COPD cases were 212.3 million with 3.3 million deaths and 74.4 million disability-adjusted life-years (DALYs) in 2019 [2]. In India, the estimated prevalence is 7.4%. It is responsible for more than

fifty lakh deaths yearly, which is 4 times higher than that in the Western world [3]. The socio-economic implications of such a disease cannot be overlooked.

On the morbidity front, exercise limitation is the hallmark of this disease which cannot be fully explained by lung function parameters alone. Deranged chest wall mechanics, dysfunction of the diaphragm and skeletal muscles of the limbs, and cardiac abnormalities like cor pulmonale are some contributors to exercise limitation [4]. Among these, cor pulmonale heralds the onset of the rapid downhill course of the disease. However, despite prompt treatment, heart failure frequently remains refractory, and left ventricular involvement could be the possible explanation. It is well known that LV filling dynamics are influenced by right ventricular (RV) loading conditions. Abnormal patterns of LV diastolic filling have been reported in the setting of increased RV pressure and/or volume. This has also been noted in the absence of other disorders affecting LV function [5]. Still, no guidelines have thoroughly addressed this issue. Hence, the present study was conducted to examine LV dysfunction in subjects with COPD in our tertiary care referral hospital.

Materials and Methods

This was a prospective study conducted at our tertiary care hospital, from October 2014 to June 2018 involved consenting subjects, diagnosed with COPD based on post-bronchodilator FEV1/FVC <0.7 on spirometry as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Subjects who were diagnosed with acute exacerbation of COPD, who had co-existing cardiac disease, who had systemic hypertension; diabetes mellitus; dyslipidemia, who were unable to perform spirometry, who had a history of alcohol consumption >2 drinks/day in females and >3 drinks/day in males (known to cause cardiomyopathy) and who were not consenting, were excluded. Demographic, clinical, hematological, spirometric, ECG, echocardiographic, and chest X-ray data were gathered. COPD was staged as below:

Post-bronchodilator FEV1/FVC < 0.7 with

- Post Bronchodilator FEV1 ≥ 80% predicted: GOLD STAGE1 (Mild)
- 50% ≤ FEV1< 80% predicted: GOLD STAGE 2 (Moderate)
- 30% ≤ FEV1 < 50% predicted: GOLD STAGE 3 (Severe)
- FEV1 < 30%: GOLD STAGE 4 (Very severe).

the cardiologist performed 2 Dimensional Transthoracic Doppler echocardiography. Emax (E) was defined as early maximal trans-mitral flow velocity and Amax (A) was defined as late peak atrial systolic velocity. E/A was used as an indicator of LV diastolic function. LV ejection fraction was used as an indicator of LV systolic dysfunction. Left Ventricular End Systolic Diameter (LVESD) and Left Ventricular End Diastolic Diameter (LVEDD) were used as indicators of ventricular remodeling.

Grading of diastolic dysfunction

Grade 1 (mild dysfunction): E/A ratio of less than 0.75 m/s.

Grade 2 (moderate dysfunction): E/A ratio of 1-1.5 m/s and normal deceleration time (DT) (160-240 ms).

Grade 3 and 4 (severe irreversible dysfunction): E/A ratio higher than 2 m/s.

Statistical analysis

Data collected was entered in SPSS 20. A descriptive analysis was done. The chi-square test, ANOVA, and Pearson`s correlation coefficient calculation were done. p-value < 0.05 was considered significant. Approval from the institutional ethics committee was obtained.

Results

During the study period, 410 consecutive subjects with COPD were identified. 38 nonconsenting subjects, 42 subjects who couldn't perform spirometry, and 261 subjects with co-existing cardiac disease or other confounding factors were excluded. Thus, 69 eligible subjects were studied. Among them, 49 subjects were male and 20 were female. The predominant age distribution was 50-70 years. Most of the subjects belonged to GOLD stage 2 and stage 3. Among 69 subjects, 9 had normal ventricular function, and 60 had evidence of ventricular dysfunction. Out of 60 subjects, 50 (72.46%) had evidence of LV diastolic dysfunction, 5 had LV systolic dysfunction, and the remaining 5 subjects had cor-pulmonale (Table 1).

The incidence of LV diastolic dysfunction (E/A) with increasing age was not significant ($p > 0.05$). However, E-max as defined by early maximal transmitral flow velocity alone correlated well with increasing age (Table 2). Symptoms such as cough with sputum production, breathlessness, smoking status, and duration of symptoms did not correlate with LV dysfunction (Table 3). However, recent worsening of breathlessness, dizziness, and syncope were the only symptoms that had a significant statistical correlation with LVDD (Table 4).

Discussion

LV diastolic dysfunction in subjects with COPD may be due to LV pre-load and afterload abnormalities. Chest wall hyperinflation secondary to emphysema may affect LV diastolic function by impairing LV filling and pre-load [6-8]. Intrinsic positive end expiratory pressure (PEEP) is common in subjects with COPD, which is known to limit venous return. Its severity is generally proportional to the severity of hyperinflation and airway obstruction [9]. Reduction of aortic diastolic blood pressure may reduce coronary perfusion leading to sub-endocardial ischemia. Both of these effects lead to myocardial fibrosis with impaired myocardial relaxation [10]. Thus, these subjects will likely have ventricular and arterial stiffening with impaired systolic and diastolic function in the absence of overt cardiovascular disease [11]. In this context, our findings suggest a potential mechanism underscoring the excess risk of coronary heart disease and congestive heart failure (CHF) in COPD; and the possibility of a relationship between airway obstruction, arterial stiffness, and cardiovascular disease in the general population [12,13]. Also, subjects with COPD experience chronic hypoxemia, which might result in abnormalities of myocardial relaxation as a consequence of intracellular calcium transport disturbances [14]. Systemic inflammation may provide a biological link between the two entities, as COPD has been regarded as a systemic disease with various extra-pulmonary manifestations. Tumour necrosis factor alpha (TNF-α), and Interleukins 6, 18 (IL-6 and IL-18) have been implicated as the key inflammatory mediators [15].

In our study, we found that a significant proportion (72.46%) of subjects with COPD had LV diastolic dysfunction. Our findings are consistent with that of Rawy and Fathalla [16] who also found LV diastolic dysfunction to be the predominant form of LV dysfunction, being detected in 73.3% of the subjects with COPD. Vizza *et al*. [17] have observed LV systolic dysfunction in less than

5% of subjects with COPD. Malerba *et al*. [18] have observed LV diastolic dysfunction in 65% of subjects with COPD. Steinberg *et al*. [19] have found LV diastolic dysfunction in 78% of subjects with COPD. A few similar studies have been summarized in Table 5. A possible explanation for this observation might be that impaired myocardial relaxation and fibrosis (discussed above) lead to diastolic dysfunction early in the course of the disease before the subject develops systolic dysfunction.

We did not find any correlation between LV dysfunction and the presence of respiratory symptoms such as cough with expectoration, chest pain, and breathlessness, or with a duration of these symptoms (Table 3). We found a statistically significant correlation only in subjects reporting recent worsening breathlessness and complaints of the cardiovascular system such as syncope and dizziness (Table 4). It is to be noted that dizziness or syncope are not common symptoms associated with COPD. However, Gaude *et al*. [16] found a significant correlation between the presence of LV dysfunction and the duration of symptoms, though, it is unclear whether echocardiography was performed during an acute exacerbation. It may be noted that myocardial strain present in subjects who present with acute breathlessness may be a factor leading to false positive evidence of LV diastolic dysfunction [25]. In our study, ECHO was not done during acute episodes to avoid this confounding effect. Since tachycardia also influences diastolic function, ECHO was delayed till the heart rate was less than 100 bpm.

Age is a proven risk factor for LV dysfunction. We found that age didn't significantly correlate with E/A (p: 0.27) which is the indicator of LVDD. Thus, we could rule out age's influence on LV function. However, E-max alone correlated well with increasing age (Table 2) We found that with progression in stages of COPD, there was no change in E/A (Table 6). This implies that there was no proper matching between the presence of LVDD and the stage of COPD. Further, pulmonary hypertension is known to influence the left ventricular dynamics indirectly through its effects on the interventricular septum. Notably, pulmonary hypertension was not present in any of the 50 subjects with LVDD in our study. Funk *et al*. [26] and Boussuges *et al*. [4] have reported similar observations albeit in a lesser proportion of subjects. All of the above observations point to the presence of LVDD in the absence of other well-known factors commonly associated with it.

It is well established that pulmonary hypertension starts to appear in the clinical picture as the individual moves to higher grades of COPD. And hence, ECHO is not generally performed until then unless there are other medical indications. In this background, our observations suggest that performing ECHO in COPD subjects irrespective of the GOLD stage may be worth doing for timely detection of LVDD.

We did not find any significant correlation between LV dysfunction and risk factors predisposing the patients to COPD such as smoking, and a history of tuberculosis (Table 4).

Even though all patients underwent chest X-rays and ECG, these were assessed by a single expert only. Hence, we did not correlate ECHO findings with Chest X-ray or ECG.

Even though our study has limitations such as being single-centered, cross-sectional study design, small study population, we have tried to eliminate all the potential confounding factors such as systemic hypertension, type 2 diabetes mellitus which are well-known comorbid conditions associated with LV dysfunction apart from age. We followed up with three subjects who were diagnosed with COPD by spirometry and the presence of LV diastolic dysfunction on echocardiography who further underwent TMT (thread mill test) and coronary angiography. These tests were normal, essentially ruling out the cardiac cause for LVDD. However, the number of cases who underwent invasive procedures was too small to conclude. In our Tertiary Care Hospital where we have more than 750 COPD subjects under follow-up, 69 cases were selected after excluding all risk factors which have an independent correlation with LVDD. Hence findings in our study are significant enough to prove the association of COPD with LV diastolic dysfunction if not causation. Early diagnosis and timely intervention in patients with COPD reduce the risk of patients progressing to refractory cardiac failure. Hence all subjects with COPD should preferably undergo echocardiography at the earliest for evaluation of left ventricular function.

Conclusions

LV diastolic dysfunction is present in a significant proportion of subjects with COPD irrespective of the stage. Useful pointers to LVDD could be symptoms such as recent worsening of breathlessness, dizziness, and syncope. It is worth screening all COPD subjects for LV diastolic dysfunction using transthoracic echocardiography.

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Table 1. Demographic details, GOLD staging, and echocardiogram findings.

Particulars	n	%
Age (in years)		
41-50	9	13.05
51-60	25	36.23
61-70	25	36.23
>70	10	14.49
Sex		
Male	49	71
Female	20	29
GOLD staging		
Grade 1	11	15.94
Grade 2	27	39.13
Grade 3	22	31.88
Grade 4	9	13.03
ECHO findings		
Normal	09	13.06
LV diastolic dysfunction	50	72.46
LV Systolic dysfunction	5	7.24
Cor pulmonale	5	7.24

Table 2. Correlation between age and Emax.

		Emax	Age
Emax	Pearson correlation	1	-0.300*
	Sig. (2-tailed)		0.020
	N	60	60
Age	Pearson correlation	-0.300*	1
	Sig. (2-tailed)	0.020	
	N	60	60

Table 3. Correlation with duration of symptoms with presence of LV dysfunction.

		E/A	Symptoms
E/A	Pearson correlation	1	.086
	Sig. (2-tailed)		.513
	N	60	60
Symptoms	Pearson Correlation	.086	1
	Sig. (2-tailed)	.513	
	N	60	60

Table 4. Correlations of different variables with LVDD.

Variable	p-value
Age	0.270
Symptoms of respiratory system	0.280
Symptoms of cardiovascular system	
Chest discomfort	0.549
Chest pain	0.849
Pedal edema	0.549
Syncope and dizziness	0.042
Breathlessness (recently worsening)	0.050
Smoking	0.393
Tuberculosis in the past	0.177
Duration of symptoms	0.603
GOLD staging	
Stage 1	0.177
Stage 2	0.171
Stage 3	0.115
Stage 4	0.470

Table 5. Studies with observed proportions of subjects having different forms of LV dysfunction.

Authors	Number of subjects with COPD (n)	Subjects with LV systolic dysfunction (%)	Subjects with LV diastolic dysfunction (%)
Steele *et al*. [20]	120	21	60
Berger *et al*. [21]	27	10	72
Mac Nee *et al*. [22]	36	14	65
Zema *et al*. [23]	37	36	68
McCollough *et al*. [24]	417	46	78

Table 6. Analysis of variance of LV dysfunction with the grading of COPD.

ANOVA						
		Sum of squares	Df	Mean Square	F	Sig.
Emax	Between groups	0.007	3	0.002	0.110	0.954
	Within groups	1.200	56	0.021		
	Total	1.207	59			
Amax	Between groups	0.043	3	0.014	0.226	0.878
	Within groups	3.521	56	0.063		
	Total	3.563	59			
E/A	Between groups	0.057	3	0.019	0.400	0.04
	Within groups	2.661	56	0.048		
	Total	2.718	59			
LVESD	Between groups	111.890	3	37.297	0.457	0.713
	Within groups	4571.093	56	81.627		
	Total	4682.983	59			
LVEDD	Between groups	542.498	3	180.833	3.503	0.021
	Within groups	2890.902	56	51.623		