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COMPARATIVE STUDY BETWEEN BIVENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS WITH COPD AND BRONCHIAL ASTHMA DURING EXACERBATION AND STABLE CONDITIONS

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ABSTRACT

Objectives: To compare right and left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease (COPD) and bronchial asthma patients during exacerbation and in between the attacks. **Methods:** Thirty patients, 22 males and 8 females, 56 ± 10 years old, with COPD: Group I, were compared to thirty asthmatic patients, 20 males and 10 females, 55 ± 8 years old, Group II. Complete echo-Doppler study and spirometry were done to all patients during exacerbation and in between the attacks. **Results:** In group I with COPD, right ventricular wall thickness (RVWT), right ventricular end diastolic area (RVEDA) and right atrial area (RAA) were increased significantly in addition to a significant decrease in pulmonary acceleration time (ACT) and ACT/ET ratio (ET: ejection time), compared to asthmatic group II, ($P<0.05$). In group I with COPD, mitral E/A ratio was decreased and isovolumic relaxation time (IVRT) was increased significantly when compared to other studied asthmatic group II, ($P<0.05$), reflecting LV diastolic dysfunction. It was also found, In group I with COPD, right ventricular end diastolic area (RVEDA) and right atrial area (RAA) were increased significantly together with a significant decrease in pulmonary acceleration time (ACT) and ACT/ET ratio (ET: ejection time), in addition, mitral E/A ratio was decreased and isovolumic relaxation time (IVRT) was increased significantly during exacerbation when compared to in between the attacks in the same group I, ($P<0.05$). Also, there was a significant inverse correlation between FEV_1 and diastolic dysfunction parameters in group I with COPD only. **Conclusion:** RV dilatation and Doppler evidence of pulmonary hypertension and LV diastolic dysfunction were reported in all patients with COPD compared to asthmatics with more profound RV affection associated with higher pulmonary artery pressure and more impairment of diastolic function parameters during exacerbation in COPD patients. Further studies are recommended in high risk COPD patients with concomitant diabetes, hypertension or with evidence of coronary heart disease.

KEYWORDS: Chronic obstructive pulmonary disease (COPD), Spirometry, decreased and isovolumic,

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world. COPD causes significant extrapulmonary effects and is associated with comorbidities that could contribute to the severity of the disease and prognosis .The anatomical and functional relationship between the heart and lungs is so close that dysfunction of one of these systems can affect the other. Chronic congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) contribute enormously to the global burden of disease.[1] Despite the fact that both diseases represent a major challenge for healthcare providers and share some common aetiological and epidemiological factors, there is a lack of relevant studies addressing the often ignored combination of CHF and COPD and still fewer addressing the simple clinical questions of interest to physicians.[2] The significance of the right ventricular performance is recognized as one of the factors determining the clinical course and prognosis in chronic obstructive pulmonary disease (independent of severity of bronchial obstruction), a potential role of the left ventricle is, however, less studied. Right ventricular overload, as a consequence of the increase of pulmonary vascular tension, can affect the left ventricular filling profile diminishing its compliance by means of the common interventricular septum.[3] During exacerbations the pulmonary artery pressure rises to 45 to 70 mmHg due to several mechanisms that include worsening hypoxia, acidosis, and changes in pulmonary mechanics.[4] The effects of chronic obstructive pulmonary disease (COPD) on right ventricular (RV)

systolic and diastolic functions and left ventricular (LV) diastolic function have been shown. Whereas LV myocardial performance index (LVMPI), which incorporates ejection and isovolumic relaxation and contraction times and is an index of global ventricular function.[1]

AIM OF THE STUDY

To determine the prevalence of right and left ventricular diastolic dysfunction in COPD patients compared to asthmatic patients during exacerbation and in between the attacks.

SUBJECTS AND METHODS

This study was performed on sixty patients, 30 patents with COPD and 30 patients with bronchial asthma during exacerbation and between the attacks. The study was carried between January 2013 and June 2015 at Madina National Hospital, Kingdom of Saudi Arabia. All subjects were submitted to full history taking (including smoking history) and clinical examination , radiological examination (plain CXR postero-anterior and lateral views), ventilatory function tests before and after bronchodilatation on the same day as their echocardiographic study by using Fukuda Denshi Spirosift 3000, serial number 67011 spirometr. The tracings were obtained with the patients in the sitting position and the best of three trials were used for analysis.

Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL. Twelve lead surface E.C.G., Doppler Echocardiography where complete examination was done using General Electric vivid 7 ultrasound system with 2.5 MHz transducer. Patients were studied in long axis parasternal, short axis parasternal, apical four and five chambers and sub costal four chamber views.

M mode measurements

From left parasternal long axis view, the following measurements were taken according to the recommendations of the American Society of Echocardiography.[5]

- Left ventricular end diastolic dimension (LVEDD).
- Left ventricular end systolic dimension (LVESD).
- Fractional shortening (FS).
- Ejection fraction (EF).
- Interventricular septal thickness at end diastole (IVSD).
- Left ventricular posterior wall thickness at end diastole (LVPWD).
- Right ventricular anterior wall thickness at end diastole (RVWT).

Left ventricular mass index (LVMI): was derived from the formula described by Devereux et al. (1986); LV MASS (gm) = 0.80 X 1.04 {(IVSD + LVPWD +LVEDD)^3 - LVEDD^3} + 0.6. all these measurements were taken at end diastole, LV mass was divided by body surface area to determine LVMI.[3]

Right ventricular end diastolic area (RVEDA): was mapped on the screen after the identification of the blood endocardial interface of the right ventricle by planimetry from the apical four chamber view at end diastole. The end diastolic frame was identified at the onset of electrocardiographic QRS complex or at or before the initial systolic cooptation of the mitral valve in the video frame. The right ventricle (RV) was considered enlarged if RVEDA was > 20.4 cm^2.[6]

Right atrial area (RAA): was measured also from the apical four chamber view by planimetrization of right atrium (RA) at end diastole. The RA was considered enlarged if RAA> 15.3 cm^2.[6]

Doppler study

1st) Mitral flow was obtained from the apical four chamber view with the sample volume located between the tips of the mitral valve leaflets. The following measurements were taken

1. E wave: peak early diastolic flow velocity
2. A wave: peak late diastolic flow velocity
3. E/A ratio,[1]

2nd) Pulmonary Flow was obtained by placing the sample volume above the pulmonary valve away from the main pulmonary artery. The following measurements were taken

1. Acceleration time (ACT): from the onset of pulmonary velocity to its peak.
2. ACT / ET ratio: where ET is ejection time measured from the onset to the end of pulmonary velocity. A ratio < 0.32 was indicative of pulmonary hypertension.[2]

3rd) Isovolumetric relaxation time (IVRT): was measured from the end of aortic flow to the beginning of mitral flow.[5]

Exclusion criteria

Patients with a previous history of coronary heart disease, heart valve disease, symptomatic peripheral artery disease, arrhythmia, patients with renal failure, diabetes mellitus and other systemic diseases, patients with diffuse parenchymal lung diseases, lung carcinoma, or other malignancies

The ethics committee of the hospital approved the study protocol. Subjects provided a written informed consent.

Statistical analysis

Data were expressed as mean ± SD. Data from all study groups were evaluated first with a one way analysis of variance. Variables that showed significant differences were then analyzed with unpaired t test to determine the differences among the groups. Paired t test was used to determine the differences in the same group between rest and exacerbation. A least squares linear correlation was

used to examine the relationship between mitral and pulmonary flow. Pearson's correlation coefficient was used to test correlation between FEV1/ Echocardiographic data variables. P<0.05 was considered to be statistically significant. Doppler parameters and FEV1 Statistical significance was assumed at P < 0.05.

RESULTS

Table 1: Demographic data in studied groups.

	GROUP I(COPD)	GROUP II (bronchial asthma)	P VALUE
No.	30	30	
Age (years)	56 ±10	55 ±8	> 0.05
Gender(M:F)	22:8	20:10	
Height (cm)	165 ±7	166 ±6	> 0.05
Weight (kg)	71 ±6	70 ±5	> 0.05
BSA (m^2)	1.78±0.09	1.77 ±0.09	> 0.05

All values are mean ± SD, M - Male, F - Female, BSA - Body surface area.
No significant difference was found between different studied groups as regard all demographic data.

Table 2: M-mode and 2 dimensional echocardiographic measurements in studied groups.

	Group I (COPD) COPD (exacerbation)	Group II (Bronchial asthma)				
	Exacerbation	Stable	p-value	Exacerbation	Stable	p-value
LVESD (cm)	2.5 ±0.2	2.6 ±0.3	>0.5	2.6 ±0.30	2.6 ±0.32	>0.5
LVEDD (cm)	4.4 ± 0.3	4.5 ± 0.2	>0.5	4.9 ±0.30	4.9 ±0.31	>0.5
EF%	76 ±4	75 ±6	>0.5	75 ±42	75 ±40	>0.5
FS%	39 ±3	40 ±5	>0.5	39 ±43	39 ±41	>0.5
IVSd (cm)	1 ±0.2	1 ±0.3	>0.5	1 ±0.10	1 ±0.11	>0.5
LVPWd (cm)	1 ±0.10	1 ±0.11	>0.5	1 ±0.05	1 ±0.06	>0.5
LVMI (gm / m^2 /BSA)	110±4	112±5	>0.5	111 ±71	111 ±70	>0.5
RVWT(cm)	0.8 ±0.1	0.8 ±0.2	>0.5	0.6 ±0.12	0.6 ±0.14	>0.5
RVEDA (cm2)	28.7 ±1.8	25.1 ±1.5	<0.5	22.5 ± 1.1	23.5 ± 1.3	>0.5
RAA (cm2)	19.8 ±2	17.1 ±1	<0.5	15.2 ±0.8	16.2 ±0.6	>0.5

All values are mean ± SD. LVESD - Left ventricular end systolic dimension, LVEDD - Left ventricular end diastolic dimension, EF - Ejection fraction. FS - Fraction shortening, IVSd -Interventricular septal diastolic thickness, LVPWd - Left ventricular posterior wall diastolic thickness, LVMI - Left ventricular mass index, RVWT - Right ventricular wall thickness, RVEDA - Right ventricular end diastolic areas, RAA - Right atrial area.

Table 3: Doppler echocardiographic parameters in different studied groups.

Variable	GROUP 1 COPD (exac)	GROUP II ASTHMA (exac)				
	Exacerbation	stable	p-value	Exacerbation	stable	p-value
E (cm /sec)	49 ±6	68 ±5	< 0.05	88 ±7	86 ±6	>0.5
A (cm / sec)	93 ±5	82 ±4	< 0.05	75 ±4	76 ±5	>0.5
E/A ratio	0.53± 0.3	0.88± 0.3	< 0.001	1.15±0.2	1.16±0.3	>0.5
IVRT(msec)	97 ±8	79 ±5	< 0.05	42 ±6	39 ±5	>0.5
ACT (msec)	42 ±6	58 ±7	< 0.05	81 ±4	79 ±5	>0.5
ACT/ET ratio	0.13±0.1	0.16±0.2	< 0.05	0.26 ±0.2	0.25 ±0.1	>0.5

All values are mean ± SD. A- late mitral flow peak velocity, E/A ratio = ratio of early (E) to late (A) mitral flow peak velocities ,IVRT - Isovolumetric relaxation time, ACT - Acceleration time, ET- Ejection time, E-early mitral flow peak velocity.

Table 4: Doppler echocardiographic parameters in Stable COPD and stable bronchial asthma.

	Stable COPD	Stable bronchial asthma	p- value
RVWT(cm)	0.8 ±0.2	0.6 ±0.14	< 0.05
RVEDA (cm^2)	26.5 ±1.5	23.5 ± 1.3	< 0.05
RAA (cm^2)	17.9 ±1	15.01 ±0.06	<0.05
IVRT (msec)	79 ±5	39 ±5	< 0.001
ACT (msec)	58 ±7	81 ±4	< 0.001

ACT/ET ratio	0.16±0.2	0.26 ±0.2	< 0.001
E/A ratio	0.88± 0.3	1.16±0.3	< 0.05

All values are mean ± SD. RVWT - Right ventricular wall thickness, RVEDA - Right ventricular end diastolic areas , RAA - Right atrial area, IVRT - Isovolumetric relaxation time, ACT - Acceleration time, ET- Ejection time, E/A ratio = ratio of early (E) to late (A) mitral flow peak velocities.

Table 5: Doppler echocardiographic parameters in COPD during exacerbation and stable conditions.

	COPD (exacerbation)	COPD (stable)	P- value
RVEDA (cm2)	28.7 ±1.8	26.5 ±1.5	< 0.05
RAA (cm2)	19.8 ±2	17.5 ±1	< 0.05
ACT (msec)	42 ±6	58 ±7	< 0.001
ACT/ET ratio	0.13±0.1	0.16±0.2	< 0.05
E/A ratio	0.53± 0.3	0.88± 0.3	< 0.001
IVRT(msec)	97 ±8	79 ±5	< 0.001

All values are mean ± SD. All echocardiographic parameters reveal significant differences between COPD during exacerbation and stable conditions.

Table 6: Statistical correlation between FEV1 / Echocardiographic data in COPD with acute exacerbation group.

FEV1 / Echocardiographic data	R	P
E (cm /sec)	0.478	< 0.05
A (cm / sec)	0.418	< 0.05
E/A ratio	0.335	< 0.05
IVRT (ms)	0.401	< 0.05

All values are mean ± SD. FEV1 (forced expiratory volume of first second). There is statistical significant positive correlation between FEV1 / Echocardiographic data.

Table 7: Statistical correlation between FEV1 / Echocardiographic data in stable COPD group.

FEV1 / Echocardiographic data	R	P
E (cm /sec)	.257	0.05
A (cm / sec)	.226	0.05
E/A ratio	.110	0.05
EDT (ms)	.357	0.05

All values are mean ± SD. This table shows that there is statistical significant positive correlation between FEV1 / Echocardiographic data in stable COPD group.

Table 8: Statistical correlation between FEV1 / Echocardiographic data in bronchial asthma with exacerbation group.

FEV1 / Echocardiographic data	r	P
E (cm /sec)	.068	0.05
A (cm / sec)	.018	0.05
E/A ratio	.015	0.05
IVRT (msc)	.031	0.05

All values are mean ± SD. This table shows that there is no statistical significant correlation between FEV1 / Echocardiographic data in bronchial asthma with exacerbation group.

Table 9: Statistical correlation between FEV1 / Echocardiographic data in stable bronchial asthma group.

FEV1 / Echocardiographic data	r	P
E (cm /sec)	.038	0.05
A (cm / sec)	.012	0.05
E/A ratio	.011	0.05
EDT (ms)	.028	0.05

All values are mean ± SD. This table shows that there is no statistical significant correlation between FEV1 / Echocardiographic data in stable bronchial asthma group.

DISCUSSION

Diastolic dysfunction was defined by the presence of relaxation, filling, or distensibility abnormalities of the left ventricle on transthoracic echocardiogram.[7] The present study revealed that, In group I with stable COPD, right ventricular wall thickness (RVWT), right ventricular end diastolic area (RVEDA) and right atrial area (RAA) were increased significantly in addition to a significant decrease in pulmonary acceleration time (ACT) and ACT/ET ratio (ET: ejection time), compared to stable asthmatic group II, (P<0.05). Reflecting pulmonary hypertension RV dilatation and RV diastolic dysfunction were reported in all patients with COPD compared to asthmatics patients Our results in agreement with the study done by Anna etal. 2015 who concluded that, in stable COPD patients have moderate abnormality of the diastolic function of the RV and the increase of the RV frontal wall thickness are observed, not reaching the diagnostically significant level (>5.0 mm).while in case of de-compensated COPD there was evidence of the progressive reduction of the myocardial contractive capacity of the RV and the onset of its systolic dysfunction .These results can be explained by chronic hypoxia likely plays a role in the pathogenesis of pulmonary hypertension(PH) in COPD by inducing vascular remodeling. Hypoxic vasoconstriction may become increasingly significant during exercise due to

decreased mixed venous partial pressure of oxygen. Hypercarbia and acidosis may also cause elevations in pulmonary artery pressure either by amplification of hypoxic vasoconstriction or by stimulating hyperventilation.[9,10] Also, it has been proposed that, in emphysema, loss of tethering effect from reduced lung elastic recoil is partly responsible for the development of PH and subsequent RV dysfunction.[11] In group I with stable COPD, mitral E/A ratio was decreased and isovolumic relaxation time (IVRT) was increased significantly when compared to other studied stable asthmatic group II, ($P<0.05$), reflecting LV diastolic dysfunction. These results in agreement with study done by Huang etal 2014 who, concluded that, patients with COPD had a higher frequency of LV diastolic dysfunction and heart failure with preserved ejection fraction. Results suggest that early-stage COPD may have an impact on the LV diastolic function. Severe COPD mainly affected right ventricular function but there was no difference among different stages of COPD. Boussuges etal 2000 found a high frequency of LVDD in patients with COPD (76%) Funk etal 2008 also reported a prevalence rate of LVDD in COPD patients is more than 50% Gupta etal. 2011 showed diastolic dysfunction in 47.5% of patients with COPD, and only 27.5% of their patients had severe/very severe COPD Caram etal. 2013 showed more frequent echocardiographic findings of mild LVDD (88%) in COPD patients, independently of COPD stage. In the last decade, prior studies mainly focused on the relationship between LVSD right ventricular dysfunction and COPD, but few studies evaluated LVDD and COPD. LVDD can be asymptomatic or associated with heart failure symptoms.[17] The potential pathophysiologic mechanism for the association between COPD and LVDD, could be systemic inflammation as inflammation is considered to be one of the systemic manifestations of COPD. Indeed, inflammation can promote atherosclerotic plaque formation, which is associated with myocardial ischemia and LVDD Haung etal. 2014. Furthermore, the presence of cor pulmonale secondary to pulmonary hypertension can lead to interventricular septum deviation toward the left ventricle, which could alter LV structure and delay filling compliance.[18] This mechanism could explain why COPD severity and exacerbation was associated with worse diastolic function. Besides the two possible mechanisms indicated earlier, LVDD in patients with COPD may be due to abnormal pathophysiological changes in LV preload and/or afterload. Thoracic cavity hyperinflation secondary to emphysema may impair LV filling (preload) and further affect LV diastolic function.[9] In the meantime, a relationship between LV diastolic filling and emphysema has also been observed in patients with mild flow obstruction (without hyperinflation).[19] This means that the pathogenic causes of impaired LV filling are likely to be multifactorial. The earlier return of reflected arterial wave can increase LV afterload, while the concomitant reduction of aortic diastolic blood pressure may lead to subendocardial ischemia. These effects can act together to affect myocardial relaxation.[10] Elmasry etal. 2006 concluded that a transient reversible change in the transmitral inflow velocity patterns in children in acute severe asthma, which appears related to elevation of pulmonary artery pressure and deterioration of spirometric functions, they believed that this is a reflection of altered LV preload secondary to the effect of altered lung mechanics on the right sided structures and altered right ventricular function, rather than a reflection of altered intrinsic LV diastolic functions. Elmasry etal.2006 demonstrated that, during an attack of acute severe asthma in children, peak E velocity was lower, E deceleration time shorter, Peak A velocity higher, E/A ratio lower, and IVRT longer than after its resolution. This pattern of diastolic filling is consistent with slower LV isovolumic pressure fall, decreased early diastolic filling and increased filling with atrial contraction,[21] and a shift in the proportion of blood entering the LV away from early diastole to late diastole. Although this pattern is usually taken as indicative of impaired LV relaxation,[22] it can also be consistent with decreased LV preload.[23] Sobhy etal. 2013 concluded that, a more deleterious effect was found that severe asthmatic cases suffered more impairment in diastolic functions of the right ventricle than mild and moderate cases, which means that patients with bronchial asthma have right ventricular diastolic dysfunction and the degree of this dysfunction is related to the severity of the disease. The difference between the present and previous studies might be due to different distribution of disease severity, age and sex .In our study we also found, In group I with COPD, right ventricular end diastolic area (RVEDA) and right atrial area (RAA) were increased significantly together with a significant decrease in pulmonary acceleration time (ACT) and ACT/ET ratio (ET: ejection time), in addition, mitral E/A ratio was decreased and isovolumic relaxation time (IVRT) was increased significantly during exacerbation when compared to in between the attacks in the same group I, ($P<0.05$).Diastolic dysfunction in patients with frequent COPD exacerbations may be related to an increase in right ventricular volume and pressure, interventricular septal shift towards the LV, and increased thoracic pressure causing impaired LV filling.[25] Inflammation can promote atherosclerotic plaque formation, which is associated with myocardial ischemia and LVDD. Haung etal. 2014. Chronic hypoxia likely plays a role in the pathogenesis of PH in COPD by inducing vascular remodeling. Hypoxic vasoconstriction may become increasingly significant during exercise due to decreased mixed venous partial pressure of oxygen. Hypercarbia and acidosis may also cause elevations in pulmonary artery pressure either by amplification of hypoxic vasoconstriction or by stimulating hyperventilation.[9.10] This mechanism could explain why COPD severity and exacerbation was associated with worse diastolic function. Thoracic cavity hyperinflation secondary to emphysema may impair LV filling (preload) and further affect LV diastolic function.[9] These effects can act together to affect myocardial relaxation.[10] In our study

there was a significant inverse correlation between FEV1 and diastolic dysfunction parameters in group I with COPD only during stable and exacerbation conditions. Another study by Lopez etal.2011 focused on outpatients with severe COPD (FEV1 of 30%–50%), and showed a potentially highest prevalence of LVDD (90%) in patients with severe stable COPD. Watz and coworkers 2010 postulates that the effects of lung hyperinflation on increasing intrathoracic pressure and subsequent decrease in venous return to the heart may help explain the decrease in filling pressures Another study found an association between residual volume and LV mass and hypothesized that hyperinflation by augmenting LV wall stress leads to increased LV stroke work and eventually increased LV mass.[22] Others have discussed the role of hemodynamic effects of hypoxia and vascular remodeling leading to pulmonary hypertension with subsequent effect on RV and LV interdependence as a cause of altered cardiac chamber size. All of these proposed mechanisms rely on the presence of advanced lung disease to cause the cardiac changes described.[27,28]

CONCLUSION

There is a high frequency of LVDD in hospitalized patients with COPD, and LVDD may occur at the early stages of COPD, prior to changes in right ventricular function and pulmonary hypertension. In hospitalized elderly patients with COPD, LVDD should be taken into account besides right ventricular function. Closer co-operation between pulmonologists and cardiologists is necessary to optimize the management of this large population of patients.

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