Left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease (COPD), prevalence and association with disease severity: Using tissue Doppler study

Abeer M. Rawy a,*, Diaa Fathalla b

a The Department of Chest, Faculty of Medicine, Benha University, Egypt
b The Department of Cardiology, Faculty of Medicine, Tanta University, Egypt

Received 28 March 2015; accepted 23 June 2015
Available online 7 July 2015

Abstract Background: Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. It has some significant extra pulmonary effects that may contribute to its severity in individual patient. Among COPD patients, cardiovascular diseases (CVD) are responsible for approximately 50% of all hospitalizations and 20% of all deaths. Left ventricular diastolic dysfunction (LVDD) is a frequent condition in COPD patients. Inflammation is considered to be one of the systemic manifestations of COPD and provides an alternative hypothesis to explain the relationship between airflow limitation and cardiovascular risk. The present study aimed to assess the prevalence of LV diastolic dysfunction in COPD patients and its relation to the disease severity and presence of inflammatory markers.

Patient and methods: Forty nine (49) COPD patients were included in this study. All patients were subjected to full medical history, physical examination, chest roentgenogram, spirometry, laboratory blood testing for inflammatory mediators (C-reactive protein, matrix metalloproteinase-9 and tissue inhibitor metalloproteinase-1) and Echo Doppler study (conventional and tissue Doppler analysis).

Results: The results showed that 36 COPD patients had LVDD (73.3%). There was a good correlation between LVDD parameters and COPD severity across GOLD stages and inflammatory markers. MMP-9 was statistically high in COPD patient with increasing severity with a...
Background

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. It has some significant extra pulmonary effects that may contribute to its severity in individual patient [1]. COPD is considered as a major cause of respiratory morbidity and mortality world-wide and reported to be fourth-leading cause of chronic morbidity and mortality worldwide [2]. The best-recognized comorbidities in COPD include lung cancer, cardiovascular diseases, malnutrition involving primarily the loss and dysfunction of skeletal muscles, osteoporosis, anemia, diabetes, increased gastroesophageal reflux, metabolic syndrome, obstructive sleep apnea, depression, and anxiety [3]. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree, and pathologic changes, a characteristic of COPD, are found in the proximal large airways, peripheral small airways, lung parenchyma, and pulmonary vasculature. A part from these local effects, smoking may significantly contribute to or cause systemic inflammation including the stimulation of the hematopoietic system with polymorph nuclear leukocyte release, the generation of systemic oxidative stress, and the endothelial dysfunction of peripheral vessels. These systemic effects due to smoking may account for the frequent concurrent presence of other chronic illnesses such as cardiovascular diseases and metabolic disorders in COPD patients [4].

Among COPD patients, cardiovascular diseases (CVD) are responsible for approximately 50% of all hospitalizations and 20% of all deaths [5]. However, population-based studies have suggested that regardless of smoking status, age or sex, a COPD diagnosis increases the risk of cardiovascular morbidity and mortality by approximately two folds [6]. Left ventricular diastolic dysfunction (LVDD) is a frequent condition in COPD patients. Inflammation is considered to be one of the systemic manifestations of COPD and provides an alternative hypothesis to explain the relationship between airflow limitation and cardiovascular risk [7–9]. However, the prevalence of LVDD in COPD patients according to inflammatory markers and disease severity has not yet been established in COPD patients [10]. Given the prognostic implications of cardiovascular disease in COPD, its detection could serve as a guide to appropriate treatment and eventually improve survival.

Echocardiographic evaluation of left and right ventricular function in patients with COPD is really challenging, mainly due to lung hyperinflation but may be improved using tissue Doppler echocardiography (TDE) to study regional systolic and diastolic function, myocardial and annular velocities to allow precise and quantitative measurement of myocardial function and can therefore detect subclinical changes [11].

COPD is characterized by chronic inflammation with increased levels of inflammatory markers as serum CRP and matrix metalloproteinases (MMPs). MMPs are a family of calcium-dependent, zinc-containing endopeptidases that are structurally and functionally related [12]. They are secreted in an inactive (latent) form, which is called azymogen or a pro-MMP. These latent MMPs require an activation step before they are able to cleave extracellular matrix (ECM) components [13]. Recent studies have shown that levels of MMPs, especially MMP-9, are elevated in the bronchial alveolar lavage (BAL) fluid from patients with COPD, compared to normal controls [14,15], and high levels of both MMP-9 and its cognate inhibitor TIMP-1 have been found in sputum from chronic bronchitis [16] and correlated with a decrease in lung function [17,18]. MMP-9 may play important physiologic roles in lung extracellular matrix remodeling and repair, and in regulating the lung inflammatory response to injury [19]. However, MMP-9 has also been implicated in the pathogenesis of various lung diseases including chronic obstructive pulmonary diseases [14,20,21].

The present study aimed to assess the prevalence of LV diastolic dysfunction in COPD patients and its relation to the disease severity and with high levels of inflammatory markers (serum CRP, MMP-9 and TIMP-1).

Patients and methods

Patients

Forty-nine (49) COPD patients were recruited from the Pulmonary Outpatient Clinic aged > 35 years. The severity was categorized according to FEV1% of predicted referred to GOLD classification [1] to GOLD I (mild including 6 patients), GOLD II (moderate including 25 patients), GOLD III (sever including 15 patients) and GOLD IV (very sever including 3 patients). The exclusion criteria included a primary diagnosis of other respiratory diseases e.g., asthma, restrictive disorders (tuberculosis sequelae or interstitial fibrosis), sleep apnea/hypopnea syndrome or lung cancer. In addition, a primary diagnosis of unstable angina, congestive heart failure (New York Heart Association class III or IV), atrial fibrillation, previous diagnosis, treatment for or evidence of arterial hypertension at the clinical examination and patients with significant valvular heart disease (more than mild aortic or mitral
Left ventricular diastolic dysfunction in patients with COPD

valve disease). Also, other chronic diseases, such as uncontrolled diabetes mellitus, kidney or liver failure and cancer were excluded. Participants who refused to take part in the study were excluded.

The diagnosis of COPD was confirmed according to the guidelines established in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1,12): a post-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.70 and an increase <12% or 200 mL in FEV1 after inhalation of a β2 agonist. COPD severity was categorized according to the GOLD classification, considering the FEV1 (% predicted) into four grades. All of them have FEV1/FVC < 70%. GOLD I is mild disease which has FEV1 ≥ 80% of predicted, GOLD II (moderate) which has 50 ≤ FEV1 < 80% of predicted, GOLD III (sever) which has 30 ≤ FEV1 < 50% of predicted and GOLD IV (very sever) in which FEV1 < 30% of predicted [1].

Methods

All patients were subjected to full medical history, physical examination, chest roentgenogram, spirometry, laboratory blood testing for inflammatory mediators (C-reactive protein, matrix metalloproteinase-9 and tissue inhibitor metalloproteinase-1) and Echo Doppler study (conventional and tissue Doppler analysis).

Pulmonary function tests

Before doing the test, ambient temperature and pressure were entered with the patient data (age in years, weight in kilograms, height in centimeters and sex) so that all results were calculated as percent of predicted (% predicted) except for FEV1/ FVC. Pulmonary function tests were done using Sensor-medics V max series, 2130 spirometer,V 6200 Autobox, 6200 DL (Sensor Medics Corporation, 22705 Savi Ranch Parkway Yorba Linda, 92887-4645 California, USA). Flow/volume loop was performed to all cases pre and 15 min after inhalation of 400 mcg salbutamol. FEV1 values were expressed in liters and as percentages of FVC. Pulse oximetry (SpO2) was assessed using an Onyx oximeter (Model 9500 Oximeter, Nonin Medical Inc., Minneapolis, MN, USA) while the patients were breathing room air.

Echocardiographic analysis

Transthoracic echochardiography (Vivid 7; GE Healthcare) was performed by one operator blinded to all other patient data. With participants positioned in the left lateral decubitus and monitored using an electrocardiographic lead, images were obtained from the parasternal views (long axis and short axis), the apical four-chamber view, and the subcostal view. All of the measurements were performed in accordance with the American Society of Echocardiography/European Association of Echocardiography recommendations [22]. All measurements were performed at end expiration as follows: (1) Right ventricle dimensions, measured in apical view. (2) Left ventricle size and wall thickness, measured in parasternal view. (3) Left atrial diameter, measured in parasternal view. Left atrial (LA) volume in systole was also measured just before the mitral valve opening, using the biplane Simpson’s method, as a mean between the values recorded in apical four- and two-chamber approaches. Subsequently, LAV was indexed for body surface area (BSA), such as left atrial volume index (LAVI) in mL/m² [23,24]. (4) Aortic root diameters, measured at the sinuses of Valsalva. (5) Left ventricular ejection fraction, assessed by Simpson’s rule when adequate two- and four-chamber views were available, Or by measuring the ejection fraction (EF) according to the Teichholz method. In other cases we applied visual estimation (“eye-balling”). (6) Evaluation of left ventricular diastolic function, which included: (i) peak velocity of early diastolic flow (E), peak velocity of atrial contraction (A), and their ratio (E/A), measured over the mitral valve. (ii) Tissue Doppler imaging measured in the lateral mitral annulus at early diastole (e1), in septal mitral annulus during diastole (e2), average mitral annular velocity during diastole average (e), and the E/e ratio [22], (iii) Diastolic function of the left ventricle was classified into four categories: normal; mild or grade I (impaired relaxation) pattern, moderate or grade II (pseudo normal filling), and severe (restrictive) filling or grade III diastolic dysfunction, following the practical approach scheme for grading diastolic dysfunction according to the combined European and American recommendations for the Evaluation of Left ventricular diastolic function by echocardiography [22]. (7) Tricuspid regurgitant velocity (TRV) recorded by continuous wave Doppler. Pulmonary hypertension was considered when TRV was ≥ 2.8 m s⁻¹ [22], and subsequently graded as mild (2.8–3.4 m s⁻¹) or moderate–severe (> 3.4 m s⁻¹) (Fig. 1).

Laboratory analysis

All samples were collected and analyzed at the same time. Serum concentrations of MMP-9 and TIMP-1 were assayed using the same batch of a commercially available kit (The Ray Bio_ human MMP-9 and TIMP-1, 3607 Parkwy Lane, Suite 100 Norcross, GA 30092) using ELISA (enzyme-linked immunosorbent assay). It is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human MMP-9 and TIMP-1 respectively. The detection reaction uses a modified pro-urokinase in which the activation sequence, normally recognized by plasmin (Pro-Arg-Phe-Lys β Ile-Ile-Gly-Gly), is replaced by a sequence specifically recognized by MMPs (Arg-Pro-Leu-Gly β Ile-Ile-Gly-Gly). The procedure was done according to manufacturer’s instruction. The results were detected from slandered curve with minimum detection value of 10 pg/ml for MMP-9 and 40 pg/ml for TIMP-1. The CRP- latex agglutination test was used for the qualitative and semi-quantitative detection of the CRP in human serum for all patients. Latex particles coated with IgG anti-human CRP were agglutinated when mixed with samples containing CRP. The CRP-latex sensitivity was calibrated to the Reference material CRM 470/RPPHS.

Statistical analysis

Patients’ characteristics and data were presented as mean ± standard deviation unless otherwise stated. Comparisons were performed by unpaired t-tests for quantitative data. We performed analysis of variance (ANOVA) for linear trend to analyze the differences inflammatory markers and echocodoppler variables across the GOLD stages. Pearson
correlations were performed to analyze the associations between lung function and echo doppler variables and inflammatory markers. *P*-value of <0.05 was used to indicate differences between the groups that were statistically significant. Data analysis was performed with a commercially available statistical analysis software package (SPSS 16.0 for Windows; SPSS; Chicago, IL, USA).

**Results**

Forty-nine consecutive stable COPD patients were included in this study from the outpatient department after exclusion of other COPD who did not fill the inclusion criteria. Those patients were classified according to GOLD classifications to GOLD I, II, III and IV. This study included forty-two male patients and seven female patients. The mean age for all patients was 53.6 ± 9.6. Age and sex did not differ statistically between the groups. As the severity of COPD increased, the spirometric values became lesser with highly significant differences between groups. Inflammatory markers were statistically highly significantly different between COPD groups (Table 1).

Echocardiographic variables of systolic and diastolic functions of the patients across GOLD classes are presented in Table 2 with comparison between patients with GOLD I, II 31 patients (63.26%) in one group and III and IV 18 patients (36.73%) in the other group, patients with severe and very severe COPD have statistically significant higher LA volume, lower *E/A* ratio, lower average (*e*) values and lower *E/e* ratio if compared with patients with mild and moderate COPD (Table 2).

The results in Table 3 show that 36 COPD patients had LVDD (73.3%) with 18 patients (72%) in group 2, 15 patients (100%) in group 3 and 3 patients (100%) in group 4 (Table 3). They were divided according to LVDD severity to three grades. There were 21 patients with grade I diastolic dysfunction most of them with COPD II patients. Grade II LVDD including 12 patients and grade III LVDD was present in 3 patients (Table 4).

The results in Table 5 demonstrate that these echo variables have statistically significant correlations with FEVI across the GOLD stages and the average *e* values correlate the best with FEVI. For inflammatory markers, MMP-9 was statistically

---

**Table 1** Demographic, spirometric variables and inflammatory markers of COPD patients according to the GOLD classification.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n = 49)</th>
<th>COPD I (n = 6)</th>
<th>COPD II (n = 25)</th>
<th>COPD III (n = 15)</th>
<th>COPD IV (n = 3)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>42 /7</td>
<td>6 /0</td>
<td>19 /6</td>
<td>14 /1</td>
<td>3 /0</td>
<td>0.5</td>
</tr>
<tr>
<td>Age in years</td>
<td>53.6 ± 9.6</td>
<td>49.7 ± 10.7</td>
<td>55.1 ± 9.7</td>
<td>51.9 ± 9.6</td>
<td>57.3 ± 5.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulmonary function tests: (spirometry) Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>63.6 ± 7.7</td>
<td>69.2 ± 1.8</td>
<td>64.6 ± 6.4</td>
<td>62.98 ± 7.2</td>
<td>48.1 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.96 ± 1.03</td>
<td>3.7 ± 0.83</td>
<td>3.2 ± 1.1</td>
<td>2.4 ± 0.67</td>
<td>2.2 ± 0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>69.9 ± 17.4</td>
<td>88.2 ± 16.9</td>
<td>75.8 ± 13.8</td>
<td>56 ± 10.1</td>
<td>52.9 ± 13.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.98 ± 0.77</td>
<td>2.9 ± 0.76</td>
<td>2.14 ± 0.67</td>
<td>1.51 ± 0.41</td>
<td>1.05 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>57.66 ± 17.03</td>
<td>86.8 ± 7.2</td>
<td>63.4 ± 7.5</td>
<td>42.2 ± 4.8</td>
<td>28.9 ± 0.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SpO2</td>
<td>95.53 ± 2.27</td>
<td>98.2 ± 0.75</td>
<td>96.7 ± 1.15</td>
<td>93.5 ± 0.64</td>
<td>91 ± 1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>c-reactive protein</td>
<td>9.3 ± 3.9</td>
<td>5.9 ± 1.05</td>
<td>8.4 ± 1.23</td>
<td>10.7 ± 1.4</td>
<td>14.3 ± 1.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum MMP-9</td>
<td>239.16 ± 43.27</td>
<td>191.3 ± 7.8</td>
<td>224.8 ± 30.3</td>
<td>270.4 ± 36.8</td>
<td>298 ± 47.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>150.327 ± 33.8</td>
<td>178.3 ± 8.4</td>
<td>162.6 ± 24</td>
<td>127 ± 33.2</td>
<td>108 ± 38.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum TIMP-1</td>
<td>239.16 ± 43.27</td>
<td>191.3 ± 7.8</td>
<td>224.8 ± 30.3</td>
<td>270.4 ± 36.8</td>
<td>298 ± 47.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>178.3 ± 8.4</td>
<td>162.6 ± 24</td>
<td>127 ± 33.2</td>
<td>108 ± 38.9</td>
<td>108 ± 38.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMP-9/TIMP1</td>
<td>1.79 ± 0.92</td>
<td>1.07 ± 0.34</td>
<td>1.5 ± 0.45</td>
<td>2.4 ± 1.035</td>
<td>3.12 ± 1.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.07 ± 0.34</td>
<td>1.5 ± 0.45</td>
<td>2.4 ± 1.035</td>
<td>3.12 ± 1.53</td>
<td>3.12 ± 1.53</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
high in COPD patient with increasing severity and association of LVDD. There was a negative correlation of MMP9 and the ratio of MMP9/TIMP1 with FEV1 while there was a positive correlation of E/e ratio correlates the best with MMP9 and the ratio of MMP9/TIMP1 and TIMP-1 (Table 6).

The results in Table 6 shows there is a high statistical significant correlation between echo variables and inflammatory markers, the E/e ratio correlates the best with MMP9 and the ratio of MMP9/TIMP1 and TIMP-1 (Table 6).

**Discussion**

Cardiovascular disease is a frequent cause of mortality in COPD. Roughly 30% of COPD patients die from a cardiovascular cause [25–28]. The main findings in the current study are that there was a high prevalence (73%) of LVDD in COPD patients which is associated with increased disease severity according to GOLD classification and the presence of inflammatory markers serum MMP-9 and TIMP-1 while in other studies the prevalence was 90% [29], 50% [30] and 64% [28]. In other study the prevalence was 73.5% [31]. The difference in prevalence could be attributed to different numbers of patients and severity of disease included in each study, use of tissue Doppler for assessment of diastolic function in our study which is more accurate in detection of LVDD than conventional Doppler study used in other studies, also we excluded patients with known hypertension or uncontrolled diabetes which is a well-known etiology of diastolic dysfunction.

The mechanisms that might explain the presence of left ventricular diastolic dysfunction in COPD patients are many. First is chronic hypoxemia leading to intracellular calcium transport disturbances which might result in abnormalities of myocardial relaxation [32,33]. This mechanism usually occurs in severe cases of COPD, grade III and IV as shown in the current study (Table 1). Second is the presence of pulmonary hypertension with chronic right ventricular hypertrophy which may develop in COPD patients followed by right ventricle dilatation [34,35].

During early diastole, the ventricular septum displaces toward the left ventricular cavity and the left ventricle becomes distorted from its circular configuration. The severity of left ventricular and septal deformity depends on the transseptal pressure gradient [30]. Thirdly, the presence of emphysema and hyperinflation which has been related to impaired left ventricle filling [36,37]. This is due to increased intrathoracic pressures which may impair cardiac function by decreasing biventricular preload and increasing left ventricular afterload [38]. The fourth cause is the inflammation which is considered to be one of the systemic manifestations of COPD [39]. In the present study systemic inflammation was evaluated by measuring C-reactive protein, MMP-9, TIMP-1 and MMP9/TIMP-1. There was a tendency towards higher MMP-9 and CRP levels with higher GOLD-stage (Table 1). Indeed there were lower levels of TIMP-1 and the ratio of MMP-9/TIMP-1 with higher gold stage. There was a statistically highly significant difference of inflammatory markers between COPD grades and with increasing severity of disease. This finding could explain that MMP-9 is involved in the disease process in COPD [40]. MMP-9 has been implicated in human emphysema, with its principal effect being the destruction of the extracellular matrix, particularly elastin [41]. The protease:antiprotease hypothesis has dominated thinking regarding the pathogenesis of emphysema. CRP is the well-studied biomarker of systemic inflammation in COPD [42]. Although the majority of patients in the current study with LVDD have mild diastolic dysfunction (type 1 diastolic

**Table 2** Echocardiographic variables of systolic and diastolic functions of the patients according to COPD severity.

<table>
<thead>
<tr>
<th>Echo variables</th>
<th>All patients (n = 49)</th>
<th>COPD I (n = 31)</th>
<th>COPD II (n = 25)</th>
<th>COPD III (n = 15)</th>
<th>COPD IV (n = 3)</th>
<th>t-test</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF% Mean ± SD</td>
<td>60.14 ± 5.25</td>
<td>60.4 ± 5.8</td>
<td></td>
<td>59.8 ± 4.3</td>
<td></td>
<td>2.55</td>
<td>0.014</td>
</tr>
<tr>
<td>LA Volume ml/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>35.76 ± 2.62</td>
<td>35.71 ± 2.75</td>
<td></td>
<td>35.8 ± 2.5</td>
<td></td>
<td>3.35</td>
<td>0.002</td>
</tr>
<tr>
<td>E/A Mean ± SD</td>
<td>0.93 ± 0.44</td>
<td>0.92 ± 0.38</td>
<td></td>
<td>0.91 ± 0.5</td>
<td></td>
<td>0.79</td>
<td>0.43</td>
</tr>
<tr>
<td>Average (e): Mean ± SD</td>
<td>7.16 ± 1.77</td>
<td>7.4 ± 1.7</td>
<td></td>
<td>6.8 ± 1.8</td>
<td></td>
<td>2.37</td>
<td>0.02</td>
</tr>
<tr>
<td>E/c: Mean ± SD</td>
<td>7.8 ± 5.6</td>
<td>7.6 ± 2.5</td>
<td></td>
<td>7.1 ± 3</td>
<td></td>
<td>2.59</td>
<td>0.03</td>
</tr>
</tbody>
</table>

EF: ejection fraction, E-wave: peak flow velocity of early diastolic filling, A wave = peak flow velocity of late atrial filling, Average e = average mitral annular tissue Doppler, E/e peak flow velocity of early diastolic filling/average mitral annular tissue Doppler velocities.

**Table 3** Morphological echocardiographic evaluation of the patients according to COPD severity.

<table>
<thead>
<tr>
<th>Echo variables</th>
<th>COPD I (n = 6)</th>
<th>COPD II (n = 25)</th>
<th>COPD III (n = 15)</th>
<th>COPD IV (n = 3)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal echocardiogram</td>
<td>6 (100%)</td>
<td>7 (28%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>13 (26.5%)</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>4 (66.7%)</td>
<td>19 (76%)</td>
<td>12 (80%)</td>
<td>3 (100%)</td>
<td>38 (77.6%)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>0 (0%)</td>
<td>18 (72%)</td>
<td>15 (100%)</td>
<td>3 (100%)</td>
<td>36 (73.5%)</td>
</tr>
</tbody>
</table>

**Table 4** Grades of LVDD in relation to grades of COPD.

<table>
<thead>
<tr>
<th>Grades of LVDD</th>
<th>Grades of COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD I (n = 6)</td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>0</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
</tr>
</tbody>
</table>
hypothesis for explaining this association between disease severity and diastolic function could be systemic inflammation. Inflammation is considered to be one of the systemic manifestations of COPD and provides an alternative hypothesis for explaining the relationship between airflow limitation and atherosclerotic plaque formation, which are two factors that are also associated with myocardial ischemia and left ventricular diastolic dysfunction. Furthermore, the presence of cor pulmonale secondary to pulmonary hypertension can lead to interventricular septum deviation toward the left ventricle, which alters left ventricular geometry and delays filling [43]. This mechanism could also explain why disease severity was associated with worse diastolic function. The cause of increased systemic inflammatory markers in COPD patients might be due to systemic hypoxia which is observed in patients with COPD, due to deterioration of lung function [44]. However, systemic hypoxia will usually occur only in severe disease.

In agreement with our results Godoy et al. [29] showed higher prevalence of LVDD among COPD patients which is associated with increased disease severity, but the prevalence was higher 88%, they did not use tissue Doppler which is more accurate in diagnosis of LVDD, they did not study the inflammatory serum marker relation to the disease severity, and also in our study we exclude patients with known hypertension or uncontrolled diabetes which may provide another etiology to LVDD rather than disease severity [29].

Ying sum et al., recently studied the impact of COPD on LVDD but in elderly > 65 years old where they were in concordance with our results they observed high frequency LVDD in COPD patients 65.5% but against our results they found no differences among different disease stages, that the LVDD is not associated with the disease severity, this may be explained that they included elderly patient > 65 years old who already may have some degree of diastolic dysfunction regardless of the disease severity [39].

Williams MJ et al., found also similar results as regards relation of MMP-9 to the development of left ventricular diastolic dysfunction as they found elevated active MMP-9 level is associated with more severe LVDD in patients with CAD and preserved systolic function, which may indicate abnormal extracellular matrix metabolism in myocardial ischemia [45].

### Limitations

The major limitations of the present study are the small sample size of the included patients, lack of the control group, single center experience.

### Conclusions

In conclusion there is a high prevalence of LVDD in COPD patients which is associated with increased disease severity according to GOLD classification and with the presence high
levels of inflammatory markers (serum MMP-9 and TIMP-1), is important to exclude decompensated heart failure during COPD exacerbation.

**Conflict of interest**

There is no conflict of interest.

**References**


