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Cardiovascular Comorbidity in Patients with Chronic Obstructive Pulmonary Disease: Echocardiography Changes and Their Relation to the Level of Airflow Limitation

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Abstract

AIM: To compare the frequency of echocardiographic changes in patients with chronic obstructive pulmonary disease (COPD) and non-COPD controls and to assess their relation to the level of airflow limitation.

METHODS: Study population included 120 subjects divided into two groups. Group 1 included 60 patients with COPD (52 male and 8 females, aged 40 to 80 years) initially diagnosed according to the actual recommendations. Group 2 included 60 subjects in whom COPD was excluded serving as a control. The study protocol consisted of completion of a questionnaire, pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses, and chest X-ray) and two dimensional (2D) Doppler echocardiography.

RESULTS: We found significantly higher mean right ventricle end-diastolic dimension (RVEDd) in COPD patients as compared to its dimension in controls (28.0 ± 4.8 mm vs. 24.4 ± 4.3 mm; P = 0.0000). Pulmonary hypertension (PH) was more frequent in COPD patients than in controls (33.3% vs. 0%; P = 0.0004) showing a linear relationship with the severity of airflow limitation. The mean value of left ventricular ejection fraction (LVEF%) was significantly lower in COPD patients than its mean value in controls (57.4 ± 6.9% vs 64.8 ± 2.7%; P = 0.0000) with no correlation with severity of airflow limitation.

CONCLUSION: Frequency of echocardiographic changes in COPD patients was significantly higher as compared to their frequency in controls in the most cases being significantly associated with the severity of airflow limitation. Echocardiography enables early, noninvasive, and accurate diagnosis of cardiac changes in COPD patients giving time for early intervention.

Introduction

Chronic obstructive pulmonary disease (COPD) is accompanied by comorbidities which have a significant impact on its prognosis. Furthermore, cardiovascular comorbidities are considered as a major cause for hospitalization and mortality in COPD patients [1], [2], [3], [4], [5], [6]. COPD affects pulmonary blood vessels, right ventricle and left ventricle leading to right ventricular dysfunction, left ventricular dysfunction, pulmonary hypertension (PH) and cor pulmonale [7].

COPD patients have two to three-fold increased risk for hospitalisation due to cardiovascular morbidity compared to patients without COPD [8]. Also, 20-30% of all patients with chronic heart failure have COPD [9], [10]. Shortness of breath and reduced effort tolerance is present in both diseases, so cardiac failure in COPD often remains unrecognised and symptoms are attributed to COPD exacerbations. The reason is that two dimensional (2D) Doppler echocardiography as a diagnostic method for heart failure is not implemented in primary care and is not a standard diagnostic procedure for pulmonologists controlling these patients [9], [11]. Mortality from cardiovascular diseases (CVD) is about 30% and in patients with mild and moderate COPD, the most common cause of hospitalisation and mortality is cardiovascular disease. Lung Health Study showed that reduction of 10% of forced expiratory volume in one second (FEV_1) value in the patients with mild and moderate COPD increases the risk of fatal cardiovascular events up to 30% and of non-fatal coronary events up to 20% [12]. As it was mentioned in the Towards a Revolution in COPD Health (TORCH) study, in patients with severe COPD, CVD

was less significant for morbidity and mortality whereas respiratory failure was the predominant factor [13]. Prevalence of pulmonary hypertension (PH) in COPD patients is estimated to 20-30% [4]. PH in COPD patients usually is mild to moderate with mean systolic pulmonary arterial pressure (sPAP) in the stable disease of 20-35 mmHg. Only 5-10% of patients with severe COPD have severe PH [14], [15]. As it was found in the National Emphysema Treatment Trial, 90.8% of COPD patients had sPAP higher than 20 mmHg and less than 5% had sPAP higher than 35 mmHg [16]. sPAP in COPD patients usually increases slowly, approximately 0.4-0.6 mmHg per year [17], [18].

We aimed to compare the frequency of echocardiographic changes in patients with chronic obstructive pulmonary disease (COPD) and non-COPD controls and to assess their relation to the level of airflow limitation.

Material and Methods

Study design and setting

Frequency and severity of echocardiographic changes registered by 2D Doppler echocardiography in initially diagnosed COPD patients and non-COPD controls were compared in cross-sectional analysis. The study was conducted at the General Hospital "8-th September", Skopje, in the period January – May 2018 as a continuum of our investigation of the impact of cardiovascular comorbidities on COPD (19). The study was approved by the Ethics Committee of the Medical Faculty at University "Sts.Cyril and Methodius", Skopje (03-2237/5/21.05.2018) [19].

Study population

The study population consisted of 120 subjects divided into two groups. Group 1 included 60 patients with newly diagnosed COPD following the actual Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Also, 60 subjects in whom COPD was excluded served as a control (Group 2). Non-COPD subjects were matched to COPD patients by sex, age, body mass index (BMI), and smoking status. Written informed consent was given by all subjects before entering the study.

Inclusion and exclusion criteria for Group 1 and Group 2 are explained in our article on carotid artery disease, and lower extremities artery disease in patients with COPD published previously [19].

Study protocol

The study workup included completion of a questionnaire, as well as pulmonary and echocardiographic evaluation.

Questionnaire

The interviewer-led questionnaire consisted of four parts, including questions on demographics, smoking history, respiratory and other symptoms in the last 12 months, as well as medical history and medication use.

The Body Mass Index (BMI) as a measure of body fat based on height and weight that applies to adult population was calculated by BMI calculator [20].

Study subjects were classified by their smoking status according to the World Health Organization (WHO) recommendations [21].

Respiratory symptoms in the last 12 months, i.e. cough, phlegm, dyspnea, wheezing, and chest tightness, were documented by the European Community for Coal and Steel questionnaire (ECCS-87), and the European Community Respiratory Health Survey (ECRHS) questionnaire [22], [23].

Pulmonary evaluation

The pulmonary evaluation included: dyspnea severity assessment, pre- and post-bronchodilator spirometry, arterial gas analysis, and chest X-ray.

Assessment of the degree of dyspnea was done using the British Medical Council Dyspnea Scale [24].

Pre-bronchodilator (baseline) spirometry included measures of forced vital capacity (FVC), FEV_1, FEV_1/FVC, and maximal expiratory flow at 75%, 50%, 25%, and 25-75% of FVC (MEF_{75}, MEF_{50}, MEF_{25}, and MEF_{25-75}, respectively) by electronic spirometer Spirobank G USB Spirometer (Medical International Research, Roma, Italy) with recording the best result from three measurements the FEV_1 values of which were within 5% of each other. The results of measurements were expressed as percentages of the predicted values following the actual recommendations of the European Respiratory Society (ERS) and ATS. Post-bronchodilator spirometry was performed 20 minutes after administration of 400 μg salbutamol by metered-dose inhaler through the spacer. Fixed airflow narrowing was considered if post-bronchodilator FEV_1/FVC value remained less than 0.70. The degree of FEV_1 reversibility was expressed as % FEV_1 reversibility ([post-bronchodilator FEV_1 – pre-bronchodilator FEV_1]/pre-bronchodilator FEV_1 x 100). Significant FEV_1 improvement (a change of more than 12% and more than 200 mL) in the presence of fixed airflow limitation did not negate a diagnosis of COPD [25].

The diagnosis of COPD was established according to the actual GOLD recommendations, i.e.,

COPD was considered by the presence of persistent airflow limitation, i.e. a post-bronchodilator FEV_1/FVC value less than 0.70, in the subjects who had dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease (noxious particles and gases, i.e. tobacco smoke, smoke from home cooking and heating fuels, and/or occupational dusts and chemicals). Also, based on the level of the airflow limitation, the COPD severity was classified as mild, moderate, severe, and very severe (GOLD 1, GOLD 2, GOLD 3, and GOLD 4, respectively) [26].

Values of the arterial blood gases were measured using the SIEMENS RAPIDPOINT 405 System (Siemens Healthineers, Australia).

Cardiovascular evaluation

Resting 2D Doppler Echocardiography was performed by a cardiologist using General Electric Vivid 7, according to the recommendations of the American Heart Association (AHA). Measured parameters included: left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVEDs), left atrial dimension (LA), left ventricular ejection fraction (LVEF %) by Teischoltz, interventricular septum (IVS), right ventricular end-diastolic dimension (RVEDd), right atrial dimension (RA), estimation of left ventricular diastolic dysfunction, measurement of systolic pressure in pulmonary artery (sPAP), wall abnormalities in right ventricle, and mitral, aortic, tricuspid and pulmonary valvular evaluation. Right ventricular dilation is present when RVEDd exceeded the normal range of 0.9-2.6 cm. Right ventricular systolic dysfunction was present when it was hypokinetic. E/A, i.e. diastolic filling of the left ventricle, was classified initially based on the peak mitral flow velocity of the early rapid filling wave (E) and the peak velocity of the late filling wave caused by atrial contraction (A). In normal subjects, LV elastic recoil is vigorous because of normal myocardial relaxation. Therefore, more filling is completed during early diastolic, so LVEDd is present when E/A value is less than 1.3 (age group 45-49 years), less than 1.2 (age group 50-59 years), less than 1.0 (age group 60-69 years), and less than 0.8 (age group aged equal or more than 70 years) (30). Pulmonary hypertension was defined as a sPAP value equal to or higher than 30 mmHg. According to the severity degree, PH is classified as mild (sPAP = 30-50 mmHg), moderate (sPAP = 50-70 mmHg) and severe (sPAP > 70 mmHg) [27], [28].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Analyses of the data included testing the differences in prevalence, comparison of the means, and testing the association mentioned above. A *P*-value of less than 0.05 was considered as statistically significant.

Results

Characteristics of the study subjects were similar in both EG and CG with the exception of the mean values of spirometric parameters which were significantly lower in COPD patients than in controls.

Table 1: Characteristics of the study subjects

Characteristic	Group 1 (n = 60)	Group 2 (n = 60)
Sex		
M	52 (86.7%)	47 (78.3%)
F	8 (13.3%)	13 (21.6%)
Mean age (yrs)		
M	65.9 ± 7.5	64.3 ± 8.1
F	67.9 ± 6.1	65.3 ± 7.4
Smoking status		
Active smokers	5 (58.3%)	37 (61.6%)
Ex-smokers	25 (41.7%)	23 (38.3%)
Pack-year smoked	66.1 ± 25.8	64.8 ± 21.5
Mean BMI value	25.8 ± 4.9	25.9 ± 3.1
Mean baseline values		
FVC (% pred)	78.8 ± 12.3	113.1 ± 19.7
FEV_1 ((% pred)	47.5 ± 17.9	90.4 ± 15.2
FEV_1/FVC ratio	0.6 ± 0.07	0.8 ± 0.04

M: male; F: female; yrs: years; BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; % pred: percentage of the predicted value.

Distribution of the COPD patients by severity of the disease based on the degree of airflow limitation in mild, moderate, severe, and very severe form was 6.7% (4/60) patients), 35% (21/60), 36.7% (22/60), and 21.7% (13/60), respectively.

Table 2: Echocardiographic changes in COPD patients classified by the level of airflow limitation

Echocardiography characteristic of all COPD patients (n = 60)	GOLD 1 FEV1 ≥ 80% pred. (n = 4)	GOLD 2 FEV1 = 50%-79% pred. (n = 21)	GOLD 3 FEV1 = 30%-49% pred. (n = 22)	GOLD 4 FEV1 < 30 % pred. (n = 13)
Normal findings	0 (0%)	0 (0%)	2 (9.5%)	2 (50%)
Mild PH	0 (0%)	3 (14.3%)	6 (27.3%)	4 (30.8%)
Moderate PH	0 (0%)	1 (4.8%)	1 (4.5%)	2 (15.4%)
Severe PH	0 (0%)	1 (4.8%)	1 (4.5%)	1 (7.7%)
Mild TR	2 (50%)	10 (47.6%)	12 (54.5%)	6 (46.1%)
Moderate TR	0 (0%)	0 (0%)	3 (13.6%)	4 (30.8%)
Severe TR	0 (0%)	1 (4.8%)	2 (9.1%)	0 (0%)
Mild PR	0 (0%)	2 (9.5%)	1 (4.5%)	1 (7.7%)
RVEDd > 26mm	1 (25%)	10 (47.6%)	13 (59.1%)	7 (53.9%)
Enlargement of RA	0 (0%)	1 (4.8%)	2 (9.1%)	2 (15.4%)
Mild MR	2 (50%)	9 (42.9%)	10 (45.4%)	6 (46.1%)
Mild AR	0 (0%)	3 (14.3%)	6 (27.3%)	3 (23.1%)
Mild MS	0 (0%)	1 (4.8%)	1 (4.5%)	0 (0%)
IVS > 12mm	2 (50%)	6 (28.6%)	14 (63.6%)	7 (53.9%)
LVEDd >56mm	0 (0%)	3 (14.3%)	3 (13.6%)	0 (0%)
LA > 40mm	2 (50%)	9 (42.9%)	8 (36.4%)	5 (38.5%)
Concentric hypertrophy of LV with diastolic dysfunction of the type-impaired relaxation	1 (25%)	3 (14.3%)	12 (54.5%)	3 (23.1%)
Impaired global systolic function of LV	0 (0%)	3 (14.3%)	2 (9.1%)	0 (0%)
Abnormal left ventricular kinetics	0 (0%)	4 (19.0%)	3 (13.6%)	0 (0%)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; PH: pulmonary hypertension; TR: tricuspid regurgitation; PR: pulmonary regurgitation; RVEDd: right ventricular end-diastolic dimension; RA: right atrial; MR: mitral regurgitation; AR: aortic regurgitation; MS: mitral stenosis; IVS: interventricular septum; LVEDd: left ventricular end-diastolic dimension; LA: left atrial; LV: left ventricle.

Registered echocardiographic changes in the subjects of Group 1 classified according to the

severity of airflow limitation are presented in Table 2. The most frequent abnormality of the right heart was increased RVEDd, whereas dilated left atrium and left ventricular hypertrophy were the most frequent left heart abnormalities. Also, TR was the most frequent valvular abnormality.

Comparison of echocardiographic findings indicated a significant difference between right heart parameters in the Group 1 as compared to their values in the Group 2. Also, except interventricular septum, there was a significant difference between the two groups (Table 3).

Table 3: Comparison of certain echocardiographic parameters in the two groups

Echocardiographic parameter	Group 1 (n = 60)	Group 2 (n = 60)	P value
LA (19.0-40.0 mm)	39.0 ± 5.3	36.4 ± 3.5	*P* = 0.0019
LV-s < 39 mm	33.6 ± 6.4	30.7 ± 2.4	*P* = 0.0013
RVEDd (7.0-26 mm)	28.0 ± 4.8	24.4 ± 4.3	*P* = 0.0000
LVEDd (35.0-56.0 mm)	50.05 ± 5.8	46.2 ± 4.1	*P* = 0.0000
IVS (7.0-12 mm)	11.1 ± 1.9	11.4 ± 1.2	*P* = 0.1032
LVEF%	57.4 ± 6.9	64.8 ± 2.7	*P* = 0.0000

LA: left atrial dimension; LV-s: left ventricular systolic dimension; RVEDd: right ventricular end-diastolic dimension; LVEDd: left ventricular end-diastolic dimension; IVS: interventricular septum; LVEF%: left ventricle ejection fraction.

As it is mentioned above, the mean value of the LVEF% in non-COPD controls was significantly higher compared to its value in COPD patients but there was no correlation with COPD severity (Table 4).

Table 4: LVEF% value about COPD severity

COPD severity	LVEF% value
GOLD 1	61.3%
GOLD 2	56.1%
GOLD 3	57.0%
GOLD 4	55.6%

COPD: chronic obstructive pulmonary disease; LVEF%: left ventricle ejection fraction; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Frequency of PH was significantly higher in COPD patients compared to its frequency in non-COPD controls (33.3% *vs.* 0%; *P* = 0.0004*).* Frequency of PH proportionally increased with FEV_1 decline (Table 5).

Table 5: Frequency of PH about the level of airflow limitation

COPD severity	Frequency of PH
GOLD 1	0%
GOLD 2	23.8%
GOLD 3	41.0%
GOLD 4	46.1%

COPD: chronic obstructive pulmonary disease; PH: pulmonary hypertension; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Discussion

Comorbidities such as cardiac disease, peripheral vascular disease, hypertension, metabolic syndrome, diabetes mellitus, osteoporosis, and psychological disorders are commonly presented in patients with COPD with great variability in reported prevalence. Besides, cardiovascular comorbidities are considered as an important cause of mortality in COPD patients [5], [6].

The present study aimed to compare the frequency of echocardiographic changes registered by resting 2D transthoracic Doppler echocardiography in COPD patients and non-COPD controls and to assess their relation to the level of airflow limitation. We performed a cross-sectional study including 120 subjects divided into two groups. The first group included 60 initially diagnosed with COPD, whereas the second group included an equal number of subjects in whom COPD was excluded complementary by their demographic characteristics to the patients with COPD. Airflow limitation in more than half of the newly diagnosed COPD patients was assessed as severe or very severe indicating delayed recognising of the disease and late-onset of adequate treatment.

Resting 2D Doppler echocardiography was done by the same cardiologist and valvular anatomy and function, left, and right ventricle size and cardiac function were assessed.

Values of the RV parameters were significantly higher in COPD patients. There was a high prevalence of PH, right atrial enlargement, RV systolic dysfunction and tricuspid regurgitation in COPD patients, and their severity increased with COPD severity. Cor pulmonale was found in 16.7% of our COPD patients which correlates with 17.5% in Gupta et al., a study [29].

TR peak gradient as a marker for indirect evidence of PH was studied in all patients. TR in the present study was found in 44.4% of the COPD patients, that is less than its frequency in the studies performed by Higham et al., (77%) and by Kassim et al., (70%) [30], [31]. The difference can be explained by several factors like the type of equipment used, the experience of the operator, the quality of the image obtained or the body habitus. Impairment of RV function and alteration of pulmonary blood vessels complicate the clinical course of COPD and correlates inversely with the survival of these patients [7].

LV systolic function was significantly higher in non-COPD controls as compared to the COPD patients. Frequency of the LV systolic dysfunction was 5.5% in the COPD patients, that was similar to its frequency reported in the Gupta study (7.5%). Abnormal LV performance in the patients with COPD may be due to hypoxemia, acidosis, concurrent coronary artery disease, and ventricular interdependence as the RV and LV share a common septum [29].

Two major factors implicated in the mortality of COPD are the severity of PH and the development of cor pulmonale. Cor pulmonale reduces the survival of up to 30% [32]. Although the true prevalence of PH in COPD is still unknown, an elevation of pulmonary

arterial pressure is reported in 20-90% of patients when measured by right heart catheterisation [29]. The level of PH has a prognostic value for COPD patients that is demonstrated in several studies. In one of them, the 5-year survival rates were 50% in patients with mild PH (20-30 mmHg), 30% in those with moderate to severe PH (30-50 mmHg), and 0% in the small group of patients with severe PH (> 50 mmHg) [30]. As a conclusion, the high level of PH is associated with poor prognosis in COPD patients [7].

PH was not detected in any subject from Group 2, whereas its frequency among COPD patients was 33%. PH frequency reported in the studies conducted by Kassim et al., and Rabab et al., was 36% and 55.6%, respectively [31], [32]. Distribution of PH in patients with moderate, severe, and very severe COPD in the present study was 23.8%, 41% and 46.1%, respectively. Increased PH prevalence following increasing level of airflow limitation is also reported in the study conducted by Gupta & Mann and Rabab i.e. the reported prevalence of PH in patients with mild, moderate, severe, and very severe COPD was 16.7%, 54.5%, 60.0% and 83.3%, respectively [29], [33].

The findings of this study are subjects of at least three limitations. Firstly, the relatively small size of the study groups may have implications on data obtained and its interpretation. Secondly, the irregular distribution of the patients with COPD by the level of airflow limitation may also impact data obtained and its interpretation. Besides, the distribution of the study subjects by sex is also unequal. On the other side, the strength of the study is echocardiographic assessment in the initially diagnosed COPD patients.

In conclusion, in a cross-sectional study on the frequency of echocardiographic changes in newly diagnosed COPD patients and their relation to the level of disease severity we found a significantly higher prevalence of echocardiographic changes in COPD patients than in non-COPD controls which were significantly related to the level of airflow limitation. Our findings indicated that echocardiographic assessment should be a constitutive part of a periodic screening of all patients with COPD to implement a combined therapeutic strategy which should reduce morbidity and mortality in these patients.

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