

Left ventricular function in patients with advanced stages of chronic obstructive pulmonary disease in correlation with GOLD classification system

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disease, with irreversible airflow obstruction, disease with high morbidity and early mortality rate. COPD is not just a disorder limited to the lungs. As the disease progresses, extra pulmonary co morbidities occur, where cardiovascular diseases are the most common. They mostly affect the right side of the heart, but sometimes changes also occur on the left side of the heart, as a result of long-term strain from the right ventricle (RV) and pulmonary hypertension which follows COPD. Material and methods: The design of our study was prospective-clinical cross-sectional study with 2 years follow up. In the study were included 94 patients with previously confirmed chronic obstructive pulmonary disease with spirometry and classified by Tiffeneau index in four gold classes. We have analyzed the values of some echocardiographic parameters that were selected as indicators of left heart function, and also we have analyzed them in relation to the progression of COPD from milder to more severe Golden classes, such as: left ventricular diastolic dimension (LvdD - mm), left ventricular ejection fraction (EF %), myocardial performance index (MPI) of the left ventricle, global longitudinal strain (Gl strain - %) of LV, diastolic function (E/e'). Echo analysis was done by Vivid 7 echo machine with a special feature to left heart chamber characteristics and function. Results: All echocardiographic parameters analyzed in our study, underline their significance in disease progression in patients with COPD and increasing Gold classes. A varies of statistical methods and parameters were used to evaluate: left ventricular diastolic dimension(mm), Ejection fraction of left ventricle (%), MPI of the left ventricle obtain by Tissue Doppler, GL strain of left ventricle (%) and E/e' in correlation of disease progression and GOLD class. Echo-parameters MPI of the left ventricle and Global longitudinal strain LV (%), progressively grow with the rise of the gold class (form I to IV). On the contrary the values of the parameters LvdD and EF% gradually decrease with the progression of the disease and gold class. Echocardiographic parameter GL strain LV % has the highest value and statistically by decreasing the values of this parameter the risk of disease progression from gold stage I/II to Gold stage III/IV is 1.570 times higher, with high statistical

significance($p < 0,01$). The calculated value of the parameter EF% is lower than 0,75, which indicates that the model of prediction is not the best one but it's acceptable.

Conclusion: COPD is a progressive disease that affects the dimensions of the right and left heart chambers, as well as the function of both chambers and the development of pulmonary hypertension. Monitoring echocardiographic parameters intended for assessment cardiac dimension and function can help to predict disease progression for timely inclusion of specific therapeutic strategies. We suggest screening of all COPD patients for cardiac assessment using echocardiography as a non-invasive and repeatable method for their follow-up.

Keywords: left heart, echocardiography, COPD

Introduction:

Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disease, with irreversible airflow obstruction, disease with high morbidity and early mortality rate. The disease itself is characterized by persistent respiratory symptoms of limited airflow as a result of permanent airway deformation and alveolar abnormalities.¹⁾

In the pathogenesis of the disease itself, the basic mechanism is a constant inflammation as a result of chronic exposure to nicotine and air pollution. All pathological changes in patients with COPD include intense inflammatory response with a range of pro-inflammatory and inflammatory cells, such as macrophages, leucocytes and epithelial cells. Basically, it is about oxidative stress and an imbalance of protease/ant protease activity with increased protease activity which results in elastic destruction and leads to faster development of emphysema with air trapping and more serious form of the disease²⁾³⁾

COPD is not just a disorder limited to the lungs. In the evolution of the disease, extra pulmonary comorbidities occur. Cardiovascular diseases are the most common. They mostly affect the right side of the heart, but sometimes changes also occur on the left side of the heart, as a result of long-term strain from the right ventricle (RV) and pulmonary hypertension which follows COPD.⁴⁾⁵⁾

As COPD progresses, more cardiovascular complications appear. The most common finding in patients with COPD is right ventricular hypertrophy with preserved systolic function. COPD results in a relatively slow process of elevation of pulmonary artery pressure creating the opportunity for adequate adaptation of the right ventricle. Increased pulmonary vascular resistance (PVR) is not so rare condition in patients with COPD. The development of pulmonary hypertension leads to RV dilatation and development of RV heart failure during the course of the disease.⁶⁾⁷⁾

Patients with more advanced stages of COPD (Gold class III/IV), have more pronounced lung changes and develop pulmonary artery hypertension, which leads to right ventricular enlargement that compromises left ventricular filling. The majority of these patients may have

preserved left ventricular size, function, and ejection fraction, which is primarily dependent on right ventricular size and volume overload⁸⁾

Patients with COPD may exhibit impaired LV geometry and reduced early diastolic filling. This mechanism is thought to be the most likely cause of reduced LV size, stroke volume, and thus left ventricular underfilling. However, LV ejection fraction by two-dimensional echocardiography may be normal despite the possible existence of LV dysfunction. This may be the cause of heart failure symptoms, so there is a need for more sensitive diagnostic tools to detect if systolic subclinical LV damage is present in patients with COPD.

There is still insufficient information on left ventricular function in patients with COPD. The aim of our study was to evaluate left ventricular function in relation of GOLD classes in patients with COPD, using echocardiographic measurements.

Material and methods

The design of our study was prospective-clinical cross-sectional study with 2 years follow up. In the study were included 94 patients with previously confirmed chronic obstructive pulmonary disease with spirometry and classified by Tiffeneau index in four Gold classes. All patients underwent complete cardiology examination. Gender, risk factors such as hypertension, diabetes, dyslipidemia and body mass index were analysed on each group.

According to spirometry (Tiffeneau index), COPD patients were divided by GOLD classification system into 4 classes: from GOLD 1 class (FEV₁>80%) to GOLD 4 where patients have severely reduced lung capacity, (FEV₁<30%):

GOLD 1 - patients with mild form of COPD (FEV₁/FVC >80%)

GOLD 2 - patients with moderate form of COPD (FEV₁/FVC 50-80%)

GOLD 3 - patients with severe form of COPD (FEV₁/FVC 30-50%)

GOLD 4 - patients with very severe form of COPD (FEV₁/FVC <30%)

Most of the patients represent GOLD class III/IV with 28 and 30 patients in each group, where male gender was dominant especially in higher GOLD stages of the disease (Table 1).

Our study included all patients over 18 years old. The average age of patients in this study was 65 years with standard deviation (SD) +/- 15.04, while the minimum and maximum age was 44 and 82, respectively. In the study, the male gender was more represented, most prominently in the IV Gold class.

Table 1. Distribution of patients in GOLD classification

gender	GOLD class								Fisher-exact test *
	1		2		3		4		
	n	%	n	%	n	%	n	%	p
male	12	66,67	10	55,56	15	53,57	27	90,00	0,009
female	6	33,33	8	44,44	13	46,43	3	10,00	
total	18	100,00	18	100,00	28	100,00	30	100,00	

All patients in our study were thoroughly examined with anamnesis, physical examination and electrocardiogram (ECG), as well as with basic and advanced echocardiographic assessment.

We have analyzed the values of some echocardiographic parameters that were selected as indicators of left heart function, and also we have analyzed them in relation to the progression of COPD from milder to more severe Golden classes, such as: left ventricular diastolic dimension (LvdD - mm), left ventricular ejection fraction (EF%), myocardial performance index (MPI) of the left ventricle, global longitudinal strain (Gl strain - %) of LV, diastolic function (E/e').

The diastolic dimension of the left ventricle was measured on a long parasternal axis on M-mode, just below the mitral valves with mitral valve tips closed.⁹⁾¹⁰⁾

Measurement of systolic function of the Left ventricle was done by Biplane method, measuring the end-diastolic and end-systolic dimension (along the inner edge of the left ventricle) using four-chamber and two-chamber window. The estimation of the ejection fraction is semi-automated with the possibility to make some echocardiographic corrections. The measured volumes are used for Simpson biplane estimation of the ejection fraction of the left ventricle.⁹⁾

The diastolic function of the left ventricle in our study group was estimated by the derived parameter E/A which is gained from the velocity of the E wave obtained by pulse wave Doppler of the mitral valve and e' wave obtained by Tissue Doppler at the base of the interventricular septum.⁹⁾¹⁰⁾We analyzed all the parameters responsible for the assessment of diastolic dysfunction(LA volume index, tricuspid regurgitation velocity, septal, lateral and average E/e' velocity), but taking into account that all were with normal values in the studied group, during the statistical processing we took only the parameter E/e' velocity.

Myocardial deformation of the left ventricle (GLS %) is estimated by the method of speckle tracking method; whereby the longitudinal function of the left ventricle is estimated. On our echo-machine, referent value for impaired longitudinal function is GLS< -18%. Three standard views are used (apical, two and four chamber view).⁹⁾

Myocardial performance index of the left ventricle or Tei index (MPI LV) it's an indicator that is used for early detection of left systolic and diastolic dysfunction. We estimated MPI by Tissue

Doppler. Valued for MPI are obtained when we place the cursor on the free wall of the left ventricle above the mitral annulus. Referent values obtained by Tissue Doppler is MPI index<0.54.⁹⁾¹¹⁾

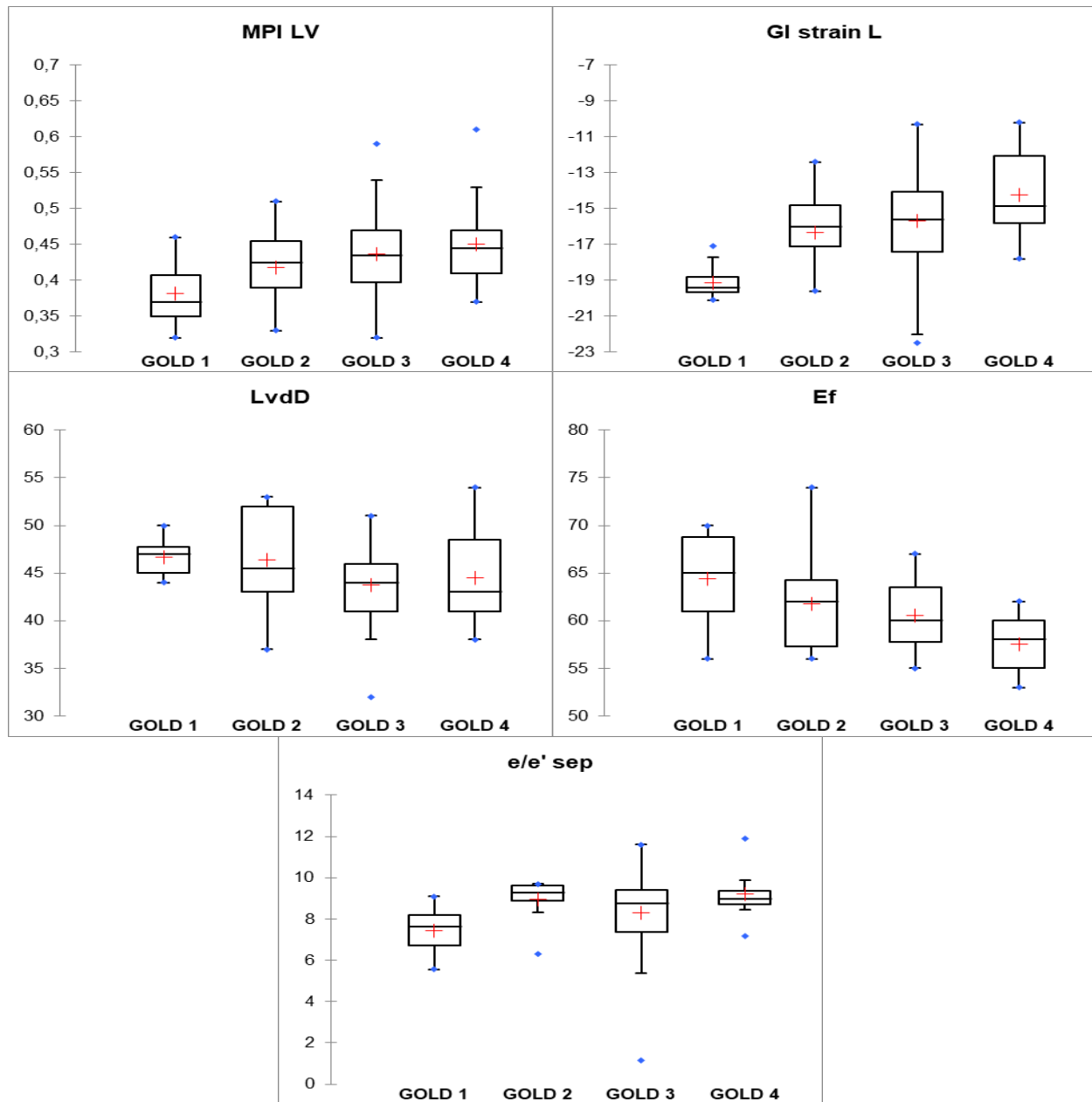
Results:

All echocardiographic parameters analyzed in our study, underline their significance in disease progression in patients with COPD and increasing Gold classes.

Echo parameters related to left ventricular loading analyzed in our study were: left ventricular diastolic dimension(mm), Ejection fraction of left ventricle (%), MPI of the left ventricle obtain by Tissue Doppler, GL strain of left ventricle (%) and E/e' in correlation of disease progression and GOLD class.

According to the obtained results, echo-parameters MPI of the left ventricle and Global longitudinal strain LV (%), progressively grow with the rise of the gold class(form I to IV). On the contrary the values of the parameters LvdD and EF% gradually decrease with the progression of the disease and gold class. While, the parameter E/e' didn't show statistical significance with the gold class in our study group.

Table 2.



According to the results obtained, there is statistically significant correlation in terms of gold class in these 4 echo-parameters: GL strain LV%, LvdD, Ef%, MPI of LV($p < 0,05$), table 2.

Table 3. Regression analysis between the values of echocardiographic parameters related to left heart load and Gold classes

parameter	average	SD	min	max	R	p
GOLD class	/	/	1	4	1	/
MPI LV	0,427	0,059	0,320	0,610	0,414	0,045
GL strain L%	-16,009	2,858	-22,500	-10,200	0,586	< 0,0001
LvdD	45,043	4,305	32,000	54,000	-0,223	0,027
Ef%	60,553	4,543	53,000	74,000	-0,534	0,001
E/e' sep	8,537	1,516	1,170	11,900	0,339	0,412

Table 4. Calculation of the risk index by logistic regression in relation to binaryGold classes in comparison of quantitative values of echocardiographic parameters related to left heart load

parameter	value	St deviation	χ^2	p	RR (95% CI)
MPI LV	15,846	4,764	11,065	0,0009	/ *
GL strain L%	0,451	0,108	17,308	< 0,0001	1,570 (1,269 - 1,941)
LvdD	-0,140	0,055	6,583	0,01	0,869 (0,781 - 0,967)
Ef%	-0,234	0,060	15,062	0,0001	0,791 (0,703 - 0,891)
E/e' sep	0,264	0,152	3,017	0,082	1,302 (0,967 - 1,753)

Additionally, binary categorization of gold classes was used in two categories: lower gold classes (1 and 2) and more advanced gold classes (3 and 4). By this statistical calculation we can confirm the highly positive correlation and high statistical significance in four echo parameters: Left ventricular diastolic dimension-LvdD,Ejection fraction of LV(EF%), MPI LV and GL strain LV%.

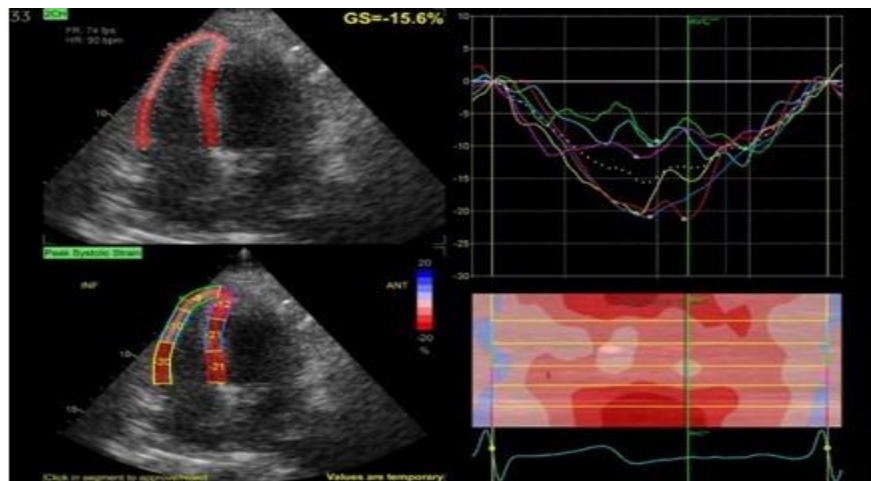
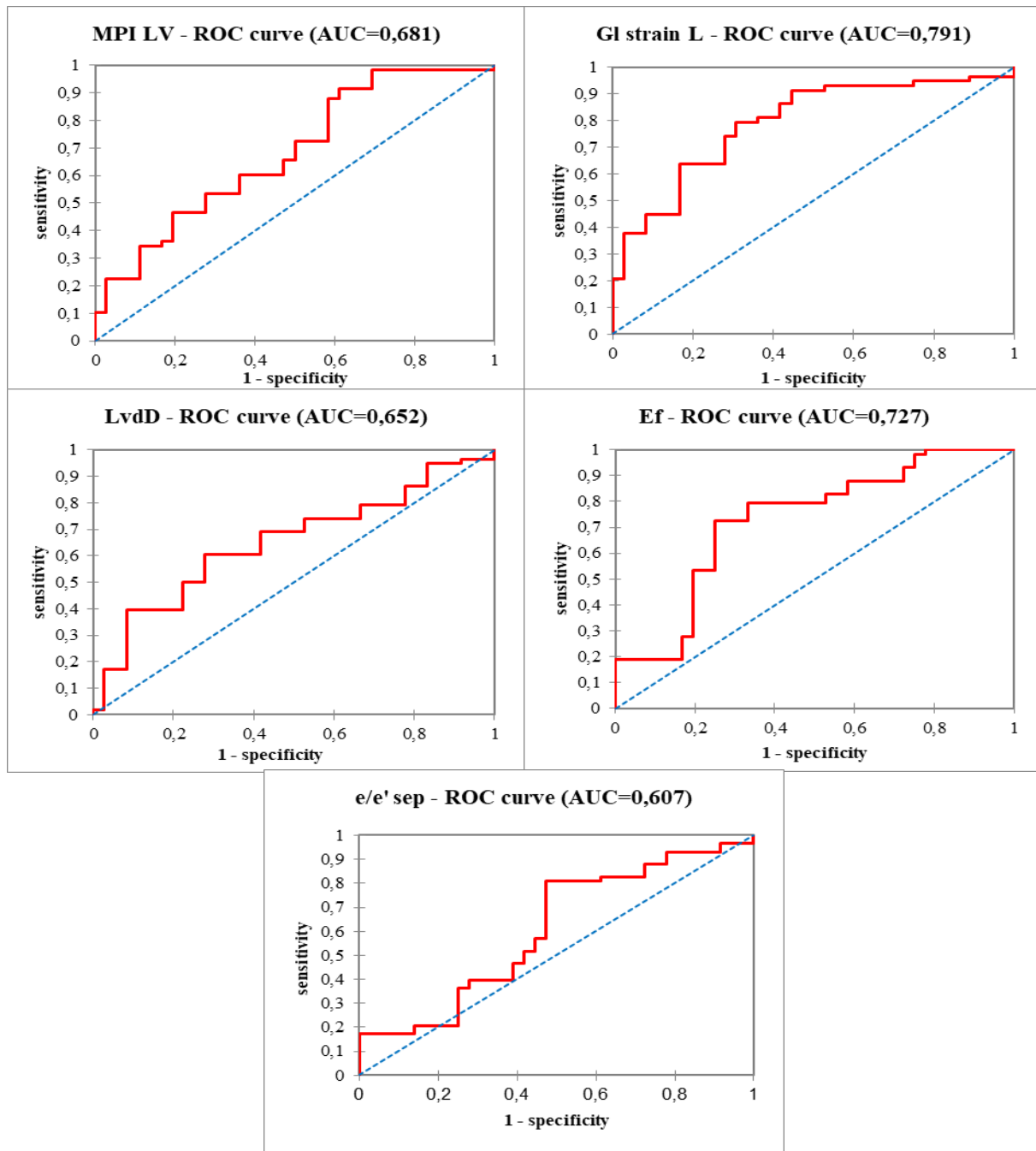


Image 1. Reduced global longitudinal strain (GS-15.6%) on the right ventricle in patient with COPD and Gold class III

Graphic 1. ROC curves obtained by logistic regression analysis of the values of five echo-parameters related to left heart loa



Echocardiographic parameter GL strain LV % has the highest value of AUC(0, 791) and statistically by decreasing the values of this parameter the risk of disease progression from gold stage I/II to gold stage III/IV is 1.570 times higher, with high statistical significance($p < 0,01$). The calculated value of the parameter EF% is lower than 0,750(0,727) which indicates that the model of prediction is not the best one but it's acceptable. The value of the relative risk(RR) from 0, 869 indicates that, the higher the values of this parameter is, the lower is the risk of COPD progression by GOLD classes, with significant statistical prediction($p < 0,01$). The rest of the echocardiographic parameters did not show a significantly high performance in predicting the gold classes according to the calculated logistic model.

Discussion:

In our study we performed a series of correlation, analyzes regarding echocardiographic parameters related to left heart function in patients with COPD. We compared our results with relevant world-wide studies.

Our study showed that the echo-parameters MPI and GL strain of LV, increase progressively with the increase of gold class, from gold class 1 to gold class 4. While the parameters diastolic dimension of left ventricle and EF% gradually decrease with the progression of the disease expressed through an increase of gold class.

COPD is a chronic inflammatory disease with aspects of irreversible bronchi obstruction and intense inflammatory response with a range of proinflammatory an inflammatory cell due to smoking and air pollution. The inflammatory process and chronic hypoxemia in patients with COPD lead to changes in pulmonary arterial trunk, loss of effective parenchyma, pulmonary fibrosis and increased pulmonary vascular resistance. Pulmonary changes take place slowly and over a long period of time, subsequently making right heart overload. Right heart overload contributes to reduction of end-diastolic dimension of LV by several mechanisms. In terms of increased right ventricular pressure and volume, interventricular septum moves toward left producing smaller left ventricular end diastolic dimension. Right ventricular dilatation causes constrictive effects on the pericardium which additionally reduces distensibility and filling of the left ventricle. Hyperinflation and emphysema in this group of patients causes hemodynamic and functional alterations which contribute to reduction of end systolic and end diastolic pressure in the left ventricle.¹²⁾¹³⁾

Patients with severe/very severe stage of COPD have right ventricular overload that causes flattening of the interventricular septum preventing complete opening of the left ventricle. All this contributes for small values for the dimension of the left atrium and ventricle.¹²⁾¹³⁾

In our study group, especially in the group of patients in gold III/IV all patients had small end-diastolic dimensions of the left ventricle and lower but still preserved ejection fraction of the LV. Left ventricular systolic function expressed as ejection fraction in all patient group is with average value of 60, 55%. Despite the duration and the severity of the disease (Gold III and IV), the left ventricular function is with preserved ejection fraction for a long time.¹²⁾¹³⁾¹⁴⁾

One meta-analysis study in 2019 (results of 15 studies), concluded that there is no deviation of ejection fraction in patients with more severe stages of COPD.¹²⁾

Patients with COPD, especially patients with emphysema, pulmonary hypertension and right ventricular overload have compressed left ventricle. Most of the patients have preserved ejection fraction of the left ventricle. Patients with more advanced form of the disease have interventricular deviation towards left specially emphasized at the end of systole and early diastole which on the other hand makes distortion of the geometries of the left ventricle and reduction in early diastolic filling of LV. Left ventricular systolic dysfunction determined through MPI and global strain of LV is highly prevalent in COPD patients without pulmonary hypertension. These results are published in a recent study 2020 with the same number of patients as in our study. Their study didn't show any significant disturbance of diastolic function. Our results are comparable with the result from the Norwegian study.¹⁴⁾

Above mentioned study where a meta-analysis on a case control study was done, indicated that patients with COPD have impaired diastolic function of the left ventricle. An extended is volumetric relaxation time, lower E/A ratio and extended deceleration time was found in this group of patients. All this is supported by the fact that there is pulmonary hiperinflation, chronic hipoxemia and hipercapnia, increased stiffness of the wall of the pulmonary arteries which contributes to diastolic dysfunction of the left ventricle.¹³⁾ Our study did not show any deterioration of diastolic function of LV through the ratio e/e' in correlation with Gold classes.

Probably the inclusion of additional echocardiographic parameters for the assessment of diastolic function in patients with COPD would explain the different interpretation (LA volume index, tricuspid regurgitation velocity, septal, lateral and average E/e' velocity) of previously mentioned studies and the results from our study.¹⁵⁾

Echo-parameter global strain of the left ventricle in our study has the highest statistical value, where decreasing values of this parameter increases the risk of progression of patients from milder to more severe stage of COPD for about 1.570 times.¹²⁾

Conclusion:

COPD is a progressive disease that affects the dimensions of the right and left heart chambers, as well as the function of both chambers and the development of pulmonary hypertension. Monitoring echocardiographic parameters intended for assessment cardiac dimension and function can help to predict disease progression for timely inclusion of specific therapeutic strategies. Left ventricular systolic dysfunction, estimated by myocardial performance index and global longitudinal strain, was highly prevalent in our study group, even in COPD patients without pulmonary hypertension. They have the most predictive value, where decrease in their value increases the risk of progression of patients from milder form of the disease to more advanced ones. Contrary to that, left ventricular end-diastolic dimension and ejection fraction gradually decline with disease progression.

We suggest screening of all COPD patients for cardiac assessment using echocardiography as a non-invasive and repeatable method for their follow-up. Larger studies for COPD patients are warranted to define the exact time and echocardiographic parameters for their follow up.

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