Original article

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EFFECT OF SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE ON THE RIGHT VENTRICULAR SYSTOLIC FUNCTION

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According to the World Health Organization, the most common complication of chronic obstructive pulmonary disease (COPD) is chronic pulmonary heart disease (*cor pulmonale chronicum*). It represents myocardial hypertrophy of the right ventricle, dilatation and insufficiency of the right ventricle occurring as a result of changes in lung function/structure in the absence of left heart disease. The gold standard in detecting changes in right heart function in patients with COPD is an echocardiographic examination. The primary goal of this research was to determine the influence of the severity of COPD on the values of the right ventricular systolic function parameter, and the secondary goal of this research was to determine the frequency of tricuspid regurgitation in relation to the degree of COPD. For a detailed assessment of the systolic function of the right ventricle, which is important for the objectives of the study, the following parameters were performed: The fractional area change (FAC) of the right ventricle and tricuspid annular plane systolic excursion (TAPSE) in 44 patients with COPD which were divided into four groups according to the global initiative for obstructive lung disease (GOLD) criteria. There was no statistically significant difference between the groups for anthropometric indicators and FEV1 values (%) ($p > 0.05$).

The Kruskal–Wallis test shows that the TAPSE index and FAC values are significantly higher in patients with severe and very severe COPD ($p < 0.05$). The results of our research show that echocardiographic parameters of the right ventricle such as TAPSE and FAC are very important for assessing its systolic function and that these values decrease proportionally with the progression of the COPD disease.

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Key words: *chronic obstructive pulmonary disease, tricuspid annular plane systolic excursion index, fractional area change*

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is progressive and is the result of airway inflammation and remodelling associated with parenchymal destruction and the development of emphysema (1). The leading risk factor for the development of COPD is the consumption of cigarettes, and in areas of air pollution, the disease has an endemic character. It occurs mainly in people over 40 years of age. Patients have symptoms more often in the morning (productive cough, dyspnea) (2).

It is estimated that 210 million people in the world suffer from COPD and that about 3 million people die from this disease every year. It is the 3rd leading cause of death in the world, and over 500,000 patients have been registered in the Republic of Serbia (2). The diagnosis of COPD is determined by a clinical examination based on symptoms, auscultatory findings and diagnostic procedures—spirometry and a post-bronchodilator test that indicates the relationship FEV1/FVC < 0.70%. Based on the The Global Initiative for Obstructive Lung Disease (GOLD) classification, it is divided into mild, moderate, severe and very severe COPD (2).

COPD is associated with significant extrapulmonary (systemic) effects, among which cardiac complications are the most common. Diseases of CVD and COPD are linked by: a large number of common risk factors (e.g. tobacco smoke in coronary disease and COPD), heart dysfunction as the last change in lung functions (primary pulmonary hypertension, increase in intrathoracic pressure), high level of inflammatory proteins in the blood (CRP) (3), disturbance of pulmonary ventilation (FEV1 and FVC), disturbance of blood gases indicating the development of hypoxia and respiratory acidosis (4), endogenous metabolic disorders and failure of neural compensatory mechanisms (5).

By increasing the resistance in the pulmonary blood vessels, changes occur in the pulmonary blood vessels and ventricles, which can lead to the development of pulmonary hypertension and chronic pulmonary heart disease, right systolic dysfunction and left ventricular diastolic dysfunction (6). According to the World Health Organization, the most common complication of COPD is chronic pulmonary heart disease (*cor pulmonale chronicum*). It represents myocardial hypertrophy of the right ventricle, dilatation and insufficiency of the right ventricle occurring as the result of changes in lung function/structure in the absence of left heart disease (7).

The gold standard in detecting changes in right heart function in patients with COPD is an echocardiographic examination. Echocardiographic characteristics of chronic pulmonary heart disease: enlarged right atrium and right ventricle, right ventricular hypertrophy, and paradoxical septum movements that occur as a result of loading the right ventricle with increased pressure in the pulmonary circulation (8, 9). To assess the function of the circumferential myocardial fibres of the right ventricle, FAC is determined, a parameter that indicates the percentage change in the area of the right ventricle in systole compared to diastole and directly correlates with the ejection fraction of the right ventricle obtained by magnetic resonance imaging.

Left ventricular dysfunction parameter values in COPD patients are often the subject of studies by pulmonologists and cardiologists around the world, and pulmonary hypertension is often investigated. However, parameters of right ventricular dysfunction are rarely examined.

Aim

The primary goal of this research was to determine the influence of the severity of COPD on the values of the right ventricular systolic function parameter, and the secondary goal of this research was to determine the frequency of tricuspid regurgitation in relation to the degree of COPD.

Material and Methods

This prospective study included 44 patients with chronic obstructive pulmonary disease. The research was conducted at the Pulmonary Clinic of the University Clinical Center in Niš in the period from January 2021 to January 2022. Patients were included in the research during regular examinations at the Pulmonary Diseases Clinic of the University Hospital Niš. During the examination, before hospitalization or previous outpatient examinations, patients were proven to suffer from COPD according to the standardized GOLD criteria (Figure 1.). Data on the clinical picture of each patient were obtained through anamnesis and clinical examination. Among the pulmonological diagnostic methods, spirometry, bronchodilator test and blood gas analysis were performed. Of the cardiological diagnostic methods, blood pressure was measured with a sphingometer, a standard 12-channel electro-cardiogram (ECG) and an echocardiographic examination were performed. All patients had their body weight and body height measured.

The criteria for inclusion in the study were: chronic obstructive pulmonary disease proven by GOLD criteria, stable phase of chronic obstructive pulmonary disease and preserved left ventricular function (LVEF > 50%).

STADIUM	DISTURBANCE OF VENTILATION	FEV1 (%)
GOLD 1	mild	≥ 80
GOLD 2	moderate	50–79
GOLD 3	severe	30–49
GOLD 4	very severe	< 30

Figure 1. Spirometric classification of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for the year 2022.

Criteria for excluding patients from the study: other lung diseases (interstitial lung diseases, pulmonary thromboembolism, lung cancer), coronary disease and recent acute myocardial infarction, hemodynamically significant heart defects, previous cardiac surgery, diabetes mellitus type I and type II, chronic renal insufficiency, reduced left ventricular function (EF < 55%), signs of left ventricular hypertrophy on ECG findings.

At the end of the regular checkup, the patients received information about the purpose and protocol of the research and signed their consent to participate in the research. Only doctors/researchers have access to data from the medical history and the results obtained from diagnostic procedures, and no information other than gender and age will be published or used for illegal purposes.

Pulmonological diagnostic methods and blood gas analysis

Arterial blood gas analyses were performed using the micromethod, by taking blood samples from the radial artery and measuring them using an AVL99 gas analyzer from the company AVL Gratz, Austria. Values of PaO2 and PaCO2 (10) were evaluated. The bronchodilator test was performed according to the recommendations of the European Respiratory Society ERS/ATS (11). Spirometric tests were performed with a pneumotachograph of the company Erich Jaeger, Würzburg, model Masterlab. The results are presented in absolute measurement units and relative measurement units (%). The following spirometric measurements were used in the diagnosis of COPD: FVC (forced vital capacity): the maximum volume of air during forced expiration, FEV1 (forced expiratory volume in the first second): the volume of air that is blown out in the first second of maximum expiration after a full inhalation. It is a measure of lung emptying rate, FEV1/FVC: FEV1, expressed as a percentage of FVC, provides a clinically useful index of airflow limitation.

In patients with a post-bronchodilator FEV1/FVC value < 70%, numbers from 1 to 4 according to the GOLD criteria provide information on the degree of reduction in the percentage value of FEV1 and limited airflow in the airways. According to the GOLD criteria, COPD is classified as a disease with mild, severe, severe and very severe ventilation disorder (12).

Cardiological diagnostic methods—Echocardiography

Standard two-dimensional echocardiography (performed on a GE Vivid 4 machine using a 2.5 MHz probe) includes a longitudinal parasternal (PLAX) (PSAX), parasternal transverse, apical, and subcostal echocardio-graphic window. Two-dimensional (2D), M-mode, continuous (CW), pulsed (PW) color Doppler and tissue Doppler were used.

For a detailed assessment of the systolic function of the right ventricle, which is important for the study objectives, the following parameters were performed: The fractional area change of the right ventricle and tricuspid annular plane systolic excursion.

Assessments of all parameters were determined by an echocardiographer according to echocardiographic guidelines (13, 14, 15). TAPSE characterizes the function of longitudinal right ventricular myocardial fibers and is measured in a four-chamber apical section by placing an M-mode cursor through the lateral tricuspid annulus, (normal values > 15 mm). FAC values are obtained by measuring the area of the right ventricle in diastole and systole using the formula Ad-As/Ad (Ad—area of the right ventricle in diastole, As—area of the right ventricle in systole) expressed as a percentage, (normal value > 35%).

Statistical analyses

In all tests, the obtained level of statistical significance was expressed, and a value of $p < 0.05$ or $p < 0.01$ was considered statistically significant, depending on the obtained results of the corresponding test. The collected data were entered into a specially created database on a personal computer, and statistical processing was done with the help of the Statistical Package for the Social Sciences (SPSS) for Windows program. The results are presented in tables and graphs with a textual commentary.

Results

The research included 44 examinees suffering from COPD (28 males and 16 females). The examinees were divided into four groups according to the severity of the disease previously determined by the GOLD criteria. There were 11 patients in each group.

The patients were from 50 to 80 years old. The average age of patients who made up the first group of subjects with a mild form of COPD was 58.70 ± 7.9, in the group of patients with decreased COPD 57.80 ± 7.5, in the group with severe COPD 61.54 ± 6.7, while in the group of patients with very severe COPD, the average age was 60.56 ± 4.4. There was no statistically significant difference in age distribution between the groups.

The anthropometric indicators of the patients are presented in Table 1 and Table 2. Table 1 shows the average values for the body mass and body height of the patients by group, while the calculated values for the body surface area and BMI are presented in Table 2. There was no significant difference for any of the values of anthropometric indicators among the groups of examinees ($p > 0.05$).

FEV1 values (%) obtained by spirometry are shown in Table 3. The Kruskal–Wallis test proved that there was a significant difference for FEV1 among all groups (p = 0.05), except for FEV1 values between the third and fourth groups.

Out of 44 patients, 7 (15.8%) had TAPSE ≤ 15 mm. In the group of patients with mild or moderate COPD, there were no patients with TAPSE ≤ 15 mm, the prevalence in severe disease was 26.67% (3 patients) and in very severe 36.67% (4 patients). There were statistically significant differences in prevalence between groups (p < 0.01). With the progression of the disease, the systolic function of the myocardium of the right ventricle decreases significantly. In terminal illness, the prevalence of decreased TAPSE, which indicates decreased systolic function of the right ventricle, is the highest.

Table 4 lists the values of the TAPSE index by group. By comparing the values of the TAPSE index using the Kruskal–Wallis test, a statistically significant difference could be observed between the second and third groups of patients, the first and fourth, as well as the second and fourth (p < 0.05).

The values for FAC are shown in Table 5. The Kruskal–Wallis test proved that FAC values were statistically significantly lower in patients with severe and very severe COPD, compared to values in patients with mild or moderate form of COPD (p < 0.05).

Table 1. Anthropometric indicators: values of body mass (kg) and body height (cm)

		TM			TV		
STADIUM		X±SD	Minimum	Maximum	X ± SD	Minimum	Maximum
I		78.73 ± 17.86	54	114	175.4 ± 9.3	158	186
II		78 .43 ± 18.4	52	119	174.05 ± 6.6	158	185
III		69.8 ± 12.8	42	96	173.2 ± 5.8	160	189
IV		68.3 ± 13.4	50	109	172.55 ± 7.4	159	186

Table 2. Anthropometric indicators: body surface area (m^2) and BMI (kg/m^2)

		TP			BMI		
STADIUM	N	X±SD	Minimum	Maximum	X±SD	Minimum	Maximum
I	11	1.99 ± 0.28	1.61	2.80	25.71 ± 4.3	19.36	33.24
II	11	1.95 ± 0.20	1.61	2.25	26.33 ± 6.5	17.70	41.52
III		1.85 ± 0.16	1.45	2.10	23.55 ± 4.1	14.52	33.06
IV		1.82 ± 0.15	1.50	2.30	23.3 ± 4.8	15.82	36.32

Table 3. FEV1 values (%)

STADIUM	N	X ± SD	Minimum	Maximum
I	11	92.87 ± 10.0	80.00	113.00
II	11	61.8 ± 7.6	50.00	78.2
III	11	32.32 ± 7.2	21.49	47.8
IV	11	27.13 ± 5.8	17.70	41.0

Table 4. TAPSE index values

STADIUM	N	X ± SD
I	11	2.05 ± 0.30
II	11	2.09 ± 0.29
III	11	1.81 ± 0.34
IV	11	1.72 ± 0.32

Table 5. FAC values (mm)

STADIUM	N	X ± SD
I	11	40.05 ± 0.30
II	11	40.09 ± 0.29
III	11	35.01 ± 0.34
IV	11	34.02 ± 0.32

Discussion

The function of the right ventricle represents an important component of the entire cardiac function. It is of prognostic and predictive significance for the origin, development and outcome of various cardiovascular diseases, non-ischemic cardiomyopathies and pulmonary hypertension (16). Changes in the pulmonary circulation often lead to diseases of the cardiovascular system, especially to the development of secondary pulmonary hypertension due to increased resistance in the pulmonary blood vessels. As a result of remodelling of the right heart, insufficiency and dilatation of the right ventricle occur over time, which in the absence of left heart disease is called cor pulmonale chronicum and is the most common complication of COPD (6, 7).

By echocardiographic examination in patients with COPD, we can determine numerous parameters of the right heart cavities used to evaluate the function of the right ventricle. In our research, the following parameters were used for a detailed assessment of the systolic function of the right ventricle: tricuspid annular plane systolic excursion, the fractional area change of the right ventricle and tricuspid regurgitation.

Kaul et al. first confirmed the use of TAPSE as a parameter of right ventricular systolic function in 1984, when a strong correlation of this parameter with right ventricular ejection fraction was established by radionucleotide angiography. TAPSE is known as tricuspid ring motion and represents the longitudinal function of the right ventricular myocardium (17). A decrease in TAPSE values in patients with COPD has been described in various studies, but the mechanism of this connection is complex and not fully elucidated (18).

According to the results of our study, the TAPSE value significantly decreases with the progression of COPD. In severe COPD, the prevalence of reduced TAPSE, which indicates reduced systolic function, is the highest ($p < 0.01$). Similar to our results, Vizza et al. described in 1998 that the drop in the ejection fraction of the right ventricle is most pronounced in patients in the terminal phase of COPD (19). In other studies, a reduced TAPSE was described in patients with COPD, only if these patients had also developed pulmonary hypertension (20). Reduced right ventricular ejection fraction assessed by TAPSE is a predictor of mortality in all patients with heart failure, regardless of the presence of COPD in the patient (21).

In 2020 and 2021, TAPSE was used as an indicator of mortality in patients with COVID-19 in several studies, the results of which were included in a systematic review of researchers from Indonesia. According to the results, for every 1 mm of TAPSE decrease, the mortality rate of patients with COVID-19 increases by approximately 20% (22). TAPSE, as a significant parameter of right ventricular systolic dysfunction, can be used to differentiate sub-massive from non-massive pulmonary embolism (23).

Measurement of right ventricular ejection fraction is an important indicator of morbidity and mortality in patients with COPD (24, 16). In addition to TAPSE, another parameter strongly correlates with EFRV: the percentage fraction of change in the right ventricular area. FAC values are obtained by measuring the area of the right ventricle in diastole and systole using the formula Ad−As/Ad (Ad—area of the right ventricle in diastole, As—area of the right ventricle in systole) expressed as a percentage. FAC less than 35% indicates right ventricular systolic dysfunction. The percentage of FAC correlates with right ventricular

ejection fraction (RVEF) measured by magnetic resonance imaging (MRI) (25).

Numerous studies have shown that a decrease in TAPSE is accompanied by a decrease in FAC (14, 26, 27, 28). In line with those results, ours show the same observations. FAC values decrease with the progression of COPD, and the lowest percentage values are found in patients with stage IV COPD ($p < 0.01$). Gosh et al. proved that the reduction of FAC according to the stages of COPD is highly proportional (29). In a study by Chen et al., it was shown that FAC and TAPSE were significantly lower in patients with COPD compared to healthy individuals. Also, it has been proven that in addition to these parameters TR, tricuspid E/A, E/e, RVMPI, RVTD and TRPG can be used to assess the change of right ventricular function in early stages (30). According to the results of the study by Ghio et al., FAC is a less reproducible measure of reduced right ventricular systolic function than TAPSE (24). These observations are probably due to the fact that the FAC measure is much more variable because it is mathematically determined on the basis of echocardiographic measures of the systolic and diastolic area of the right ventricle.

Conclusion

COPD as a disease is accompanied by a large number of extrapulmonary manifestations, among which the most frequent are cardiac manifestations. The results of our research show that echocardiographic parameters of the right ventricle such as TAPSE, FAC and TR are very important for the assessment of its systolic function and that these values decrease proportionally with the progression of the COPD disease. Based on the above results and by comparing the results of other studies, it can be concluded that an echocardiographic examination is necessary for monitoring the cardiac function of these patients and that it is necessary to introduce it routinely for COPD patients in order to reduce the load on the heart, especially the right one, keep it under control and improve the quality of life with appropriate therapy.

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UTICAJ TEŽINE HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA NA SISTOLNU FUNKCIJU DESNE KOMORE

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Prema navodima Svetske zdravstvene organizacije, najčešća komplikacija hronične opstruktivne bolesti pluća (HOBP) jeste hronično plućno srce (*cor pulmonale chronicum*); ono podrazumeva hipertrofiju miokarda desne komore, dilataciju i insuficijenciju desne komore, koja nastaje kao posledica promena funkcije/strukture pluća, u odsustvu bolesti leve strane srca. Ehokardiografski pregled je zlatni standard u otkrivanju promena funkcije desne strane srca kod obolelih od HOBP-a. Glavni cilj ovog istraživanja bio je da se utvrdi uticaj stepena težine HOBP-a na vrednosti parametara sistolne funkcije desne komore. Sporedni cilj istraživanja bio je da se odredi učestalost trikuspidne regrugitacije u odnosu na stepen HOBP-a. Radi detaljne procene sistolne funkcije desne komore, značajne za ciljeve ove studije, ispitani su sledeći parametri: procentualna frakcija promene površine desne komore (engl. *fractional area change* – FAC), trikuspidna regurgitacija (TR), amplituda sistolne pokretljivosti trikuspidnog prstena (engl. *tricuspid annular plane systolic excursion* – TAPSE) (mm). U ispitivanju su učestvovala 44 bolesnika sa HOBP-om, podeljena u četiri grupe prema GOLD (engl. *global initiative for obstructive lung disease*) kriterijumima. Nije bilo statistički značajne razlike među grupama u pogledu antropometrijskih pokazatelja i vrednosti FEV1(%) ($p > 0,05$). Na osnovu Kruskal–Wallisovog testa uočeno je da su vrednosti TAPSE indeksa i FAC-a bile značajno veće kod osoba sa teškim i veoma teškim HOBP-om ($p < 0,05$). Prilikom poređenja učestalosti TR-a u blagom HOBP-u sa onom u umerenom i u teškom HOBP-u, zapažena je statistički značajna razlika; kada je reč o ovom parametru, statistički značajna razlika postojala je i između umerenog i teškog HOBP-a ($p < 0,05$). Rezultati našeg istraživanja pokazali su da su ehokardiografski parametri desne komore, kakvi su TAPSE, FAC i TR, veoma važni za procenu njene sistolne funkcije, kao i da je opadanje ovih vrednosti srazmerno sa progresijom HOBP-a.

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***Ključne reči**: hronična opstruktivna bolest pluća, indeks amplitude sistolne pokretljivosti trikuspidnog prstena, frakcija promene površine desne komore, trikuspidna regurgitacija*