Correlation between echocardiographic parameters and the severity of stage in patients with COPD

Authors: Kjaeva Anastasova Sasha, Srbinovska - Kostovska Elizabeta, Dokic Dejan, Kjaev Ivo

Introduction

COPD is a disease of the modern society and is a cause of high morbidity, early mortality and high rate of death and a heavy burden on healthcare systems.It was on the sixth place in 1990, and it is assumed that in 2020 itis going to be one of the 3 leading causes of death worldwide [1, 2, 3].

COPD is a chronic disease, slowly progressive and is characterized with a chronic inflammation of the bronchi, which in most cases is an irreversible process. By definition, it is a chronic obstuction of the airflow as a combination of inflammation of the bronchi and bronchioli and parenchymal destruction(emphysema) [4]. Smokers are the most commonly affected subjects and as the disease progresses it leads to chronic respiratory failure. Active, passive smoking and air pollution are the main causesof disease progression. Smoking is no longer privilege of the male population; the global perception has been changed in a direction of equalization of gender smokers [2].

COPD is a disease represented in different forms: chronic bronchitis, chronic respiratory failure and emphysema [2, 4].

COPD has its first expression between the age of 40 and 50. It is characterized with air-limitation, chronic morning cough, chronic fatigue, and mucous production. COPD causes weak immune system, possibility of frequent lung infections, chest thightness, and lack of energy.

The confirmation of COPD is done by taking anamnesis of the patient, physical examination, contemporary laboratory tests (NT-proBNP), spirometry, x-ray of the lungs [5]. Patients with COPD are prone to developing cardiovascular diseases, bronchiectasis, lung cancer, osteoporosis, metabolic syndrome, muscle weakness, depressive syndome and other health conditions [6].

Early cardiovascular screening and echocardiographic evaluation of this vulnerabile group of patients with COPD will improve the quality of life and define the parameters that are crucial for monitoring this group of patients, managing the disease and reducing the need for hospitalization.

Anatomic and pathophysiologic close relationship between the respiratory and cardiovascular system as well as the present risk factors were a great motivation for conducting a thorough research in this field. COPD affects the cardiovascular system, especially the right heart function.

Patients known to have the disease for a long period have already suffered from permanent changes of the vascular bed that subsequently lead to right heart dilatation and development of right heart

failure. The right heart failure is the end-stage of the disease and results in an overall bad quality of life.

Aim

The aim of this studywas to identify the echocardiographic parameters important for evaluation of COPD patients in stage 3 and 4 according to GOLD classification.

We expect that this study will help in defining the echocardiographic parameters that are crucial for this group of patients with COPD.

Material and methods

- 22 patients (with confirmed stage of COPD) were examined and classified by GOLD classification in stage 3 and 4.
- Standard classification consists of several stages such as:
- -Stage 1 of COPD (FEV1/FVC <70%)
- -Stage 2 of COPD (FEV1/FVC<80%) GOLD II/III, divided into two subgroups
- -Stage 3 of COPD (FEV1<30%)

  Patients with coronary artery disease, congenital heart disease, cardiomyopathies (dilatata, hypertrophica), idiopathic pulmonary hypertension, asthma and pulmonary fibrosis were excluded from the study.

  This is a pilot study of the planned doctoral dissertation which is going to be a prospective (cross-sectional study) study in a two-year time interval. Recruitment of patients has started in January 2019 and is planned to be finished by the mid of 2020.The total number of planned patients to be included inthe doctoral dissertation is 100, but in this study we present the results obtained in 22 patients .
  Patients enrolled in this study were with stage 3 and 4 of COPD.
  In cooperation with the University Clinic for Pulmoallergology, all patients were classified in stages of COPD in advance (with spirometry analyses) and sent to our University Clinic for Cardiology for further examination. On admission, anamnesis, status and clinical examination, ECG and assessment of risk factors were done in every patient.
  Echocardiographic examination was done in all 22 patients with vivid 7 echomachine by general electronic. All the analyses were made on echopaque working station.
  These echofindings were analyzed:

  1.Dimensions and volumes of the left ventricle: end-dyastolic dimension of the left ventricle (LVDd), dimension of the left atrium(LA) obtained by long parasternal axis in M-mode, end-diastolic volume of the left ventricle (LVEd), end-systolic volume of the left ventricle obtained by 4 chamber view.
  2. Estimation of the muscle contaction expressed as EF (ejection fraction) in percentage obtained by simpson method.
  3. Estimation of the diastolic function of the left ventricle is expressed as E/e'relationship

In addition, attention to the parameters of the right chamber was given:

Estimation of the basal diameter of the right chamber measured by 4 chamber view in the end-diastole.

Estimation of the functional area of changes of the right chamber which gives information on the global function of the right ventricle (FAC %). It is measured by 4 chamber view and calculated as FAC(%)=100x(EDA-ESA)/EDA, which means as a difference between end-diastolic and end-systolic area divided by end-dyastolic area multiplied by 100. FAC above 35% means neat right systolic function.

-Tricuspid annular systolic excursion (TAPSE) measured by M-mode is an indicator of the longitudinal systolic function of the right ventricle. Cursor in M-mode is placed on the lateral wall of the right ventricle at the level of the tricuspid annulus in 4 chamber view. Reduction under 16 mm is one of the markers of an impaired longitudinal function of the right ventricle.

- S'wave of tissue doppler of the right chamber is more toll forevaluation of the longitudinal function. Values below 10 met/sec are a marker of an impaired longitudinal function of the right ventricle.

-Estimation of pulmonary hypertension is made by bernoulli equation: SPAP (Vmax TR)2+ pDAP (pressure that is added depending on the dimension of inferior vena cava and its collapse). Value equal or above 50mm/Hg is considered as pulmonary hypertension.

-diameter and collapse of inferior vena cava by which the pressure of the right atrium is measured

-acceleration time (AT) is calculated by pulse wave doppler through the right ventricle flow tract, and values above 105 m/sec are considered as normal.

Results

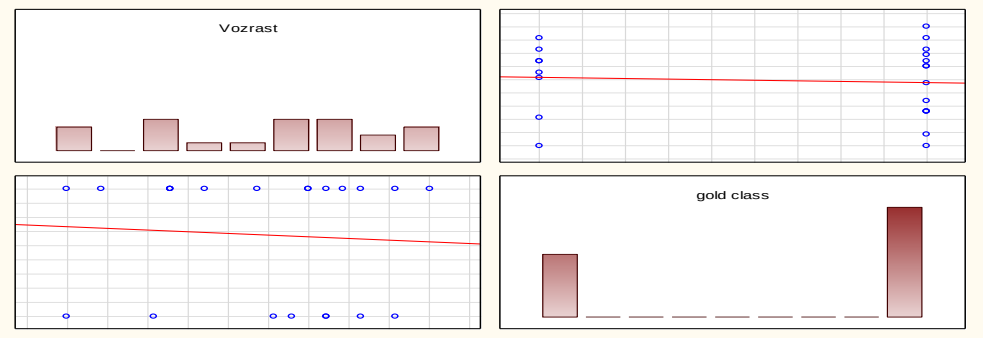
Our study included 22 patients with COPD; 17 patients were male and 5 female. The average age was 66.4+6.3, range 55 to 76 years.

Table 1. Demographic features of patients with COPD

Variables	**Average**	**Minimum**	**maximum**	**St.dev.**

age	66.4	55.0	76.0	6.30691
body weight	82.0	56.0	130.0	20.03865
height	169.1	155.0	186.0	8.98279
gender	**No**		**%**	
female	5		22.7	
male	17		77.3	

Figure 1. Correlation between age and GOLD classification:



There was a negative and weak rang correlation between age and GOLD classification (Spearman rank orders correlation)

Table 2. Stage of COPD 3/4

stage/GOLD	бpoj	%
3/ heavy stage	8	36.4
4/ very heavy stage <30%	14	63.6

All patients examined in this study were in stage 3 and 4 of COPD, but stage 4 was prevalent.

Figure 2. Stage of COPD 3/4

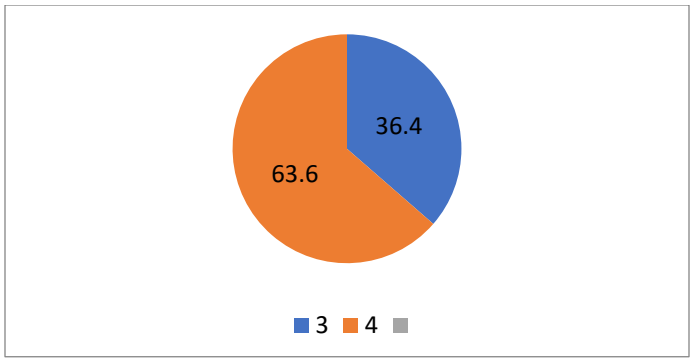


Table 3. Echocardiographic features obtained by measurment of the left atrium and ventricle

Variables/female	**N**	**average**	**minimum**	**maximum**	**St.dev.**
LVEDd	5	41.6	38.0	45.0	3.04959
LVEDvol.	5	70.6	56.0	94.0	16.22652
LVES vol	5	33.4	27.0	39.0	5.50454
variables/male					
LVEDd	17	44.4	40.0	54.0	4.31652
LVEDvol.	17	77.5	46.0	134.0	25.24163
LVES vol	17	33.7	20.0	56.0	10.79215
EF(%)	22	57,9	53	68	
E/e' sep/	22	6.9	2.7	11.9	1.88353
left atrium					
Mm	број			%	
>40	3			13.6	
<40	19			86.4	
E/e' sep/					
>8m/sec	4			18.2	
<8m/sec	18			81.8	

The average value of LVEDd (mm) was 41.6+3.0, range 38 to 45 mm,in females and 44.4+ 4.3, range 40 to 54 mm,in males.

The average value of LVED vol in female patientswas 70+16.2, range 56 to 94 ml, and 46-134.0 ml in male patients.

The average value of LVES vol in female patientswas 33.4+5.5, range 27-39 ml, and 33.7+10.8, range 20.0-56 ml, in male patients.

The analysis made in all patients showed diastolic dimension of left ventricle in both genders with low normal values as well as systolic and diastolic volume of the left ventricle.

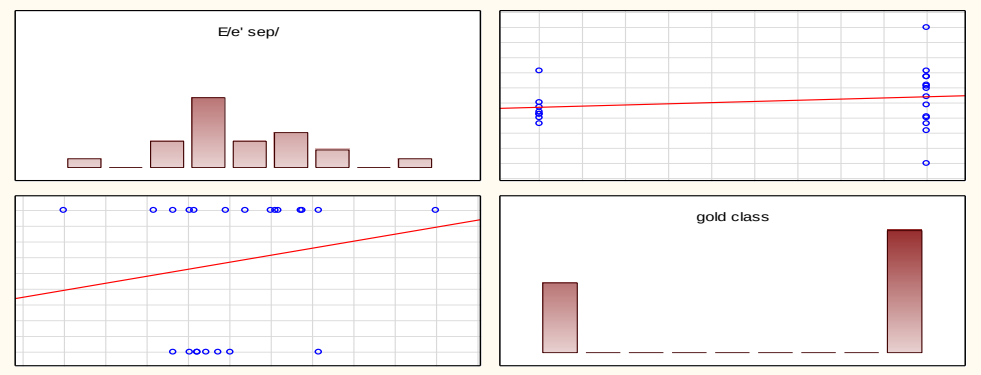
Dimensions of the left atrium above 40 mm were registered in 13.6% and below 40 in 86.4% (Table 2) of patients.In conclusion,the majority of patients were with normal dimensions of the left atrium.

Global systolic function expressed as ejection fraction (EF%) in all patients was above normal values (52%), average 57.9+4.2, range 53.0 to 68%.

Correlation between mitral flow and e' wave determined by tissue doppler showed an average value of 6.9+1.9, range 2.7 to 11.9 m/sec.Above cut-off (>8m/sec) value was registered in 4 patients (18.2%) and below cut-off values in 19 patients. The analysis of data showed that most of the patients had normal diastolic function of the left ventricle, with weak correlation between diastolic function of LV and the stage of the disease.

Dimensions of the aorta in all patients was below 38mm, average values were 32.2+2.7, range 26.0 to 37.0 mm.

Figure 3. Correlation between E/e' septal and GOLD classification



There was a weak positive rang correlation (Spearman rank order correlation) between E/e' septal and GOLD classification.

Table 4. Evaluated parameters of the right ventricle

variables	average	minimum	maxim	St. Dev.
RV base	32.0	27.0	39.0	3.255764
S TDV RV	0.09	0.07	0.1	0.010320
TAPSE	19.5	14.0	28.0	2.94076
FAC(%)	44.5	32.0	55.0	6.185446
AT a.pulm.	79.0	59.0	96.0	8.88015
SPAP	39.6	26.0	53.0	7.14249

RV base	**No**	**%**
>30mm	13	59.1
<30mm	9	40.9

S TDV RV		
>0.10	13	59.1
<0.10	9	40.9
TAPSE		
>=16mm	22	100.0
<16mm	0	
FAC(%)		
>35	20	90.9
<35	2	9.1
AT a.pulm		
<=105	22	100.0
>105	0	
SPAP		
<=50	20	90.9
>50	2	9.1

The right ventricle basal segment average value was 32.0+3.3, range 25.0-41.0 mm. Values above >30 mm, but still within reference values were found in 13(59.1%), and below 30 mm in 9(40.9%)patients.

Assessment of S wave obtained by tissue doppler above tricuspid anulus showed a starting reduction of the longitudinal function of the right ventricle. Nine of 22 patients had reduction of S wave below 0.09. According to TAPSE, which is a parameter that is used also for evaluation of the longitudinal function of the right ventricle,the average value was 19.5+2.9, range14 to 28, but all patients had values above 16 mm, which was considered as normal.

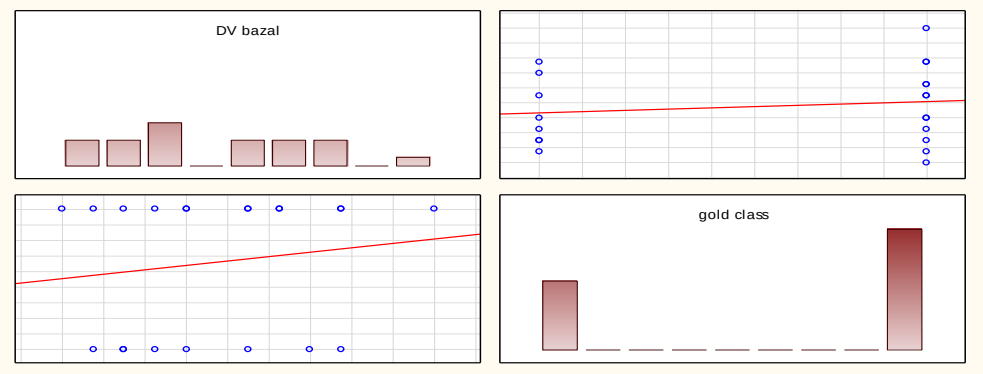
The parameter that defines the global function of the right ventricle (FAC%) had the average value of 44.5+6.2, range from 32 to 55%. Above cut-off values (35%) were registered in 21 (90.9%) patients and below cut-off values in 2 patients (9.1%).These two patients had an increased SPAP leading to development of pulmonary hypertension.

Mean artery pressure was obtained witha formula derived by maximum velocity of the tricuspid regurgitation, and the average value was 39.6+7.1, range 26 to 53. Above cut-off values (50 mm/hg) was registered in 2 patients (9.1%), and below cut-off values in 20 (90.9%) patients.

The analysis of the collapsibility of inferior vena cava in patients with COPD is one of the parameters that shows an increased pressure in the right heart cavities. In 50% of our patients non-collapse of inferior vena cavawas registered. There was a statistically significant association between GOLD and inferior vena cava insp/exp (<50%;>50%) (Fisher Exact 2 tailed test,=0.023375).

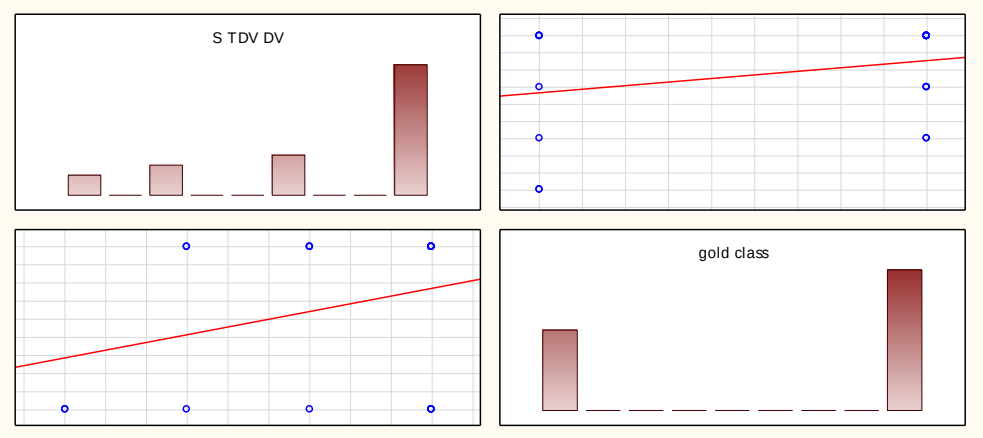
The time of acceleration (AT)obtained as a parameter from the tissue doppler record of the pulmonary artery had an average value of 79.0+8.9, ranging from 59 to 96 msec. Value below cut-off (<=105) was registered in all 22 patients (100%).

Figure 4. Correlation between RV basal and GOLD classification



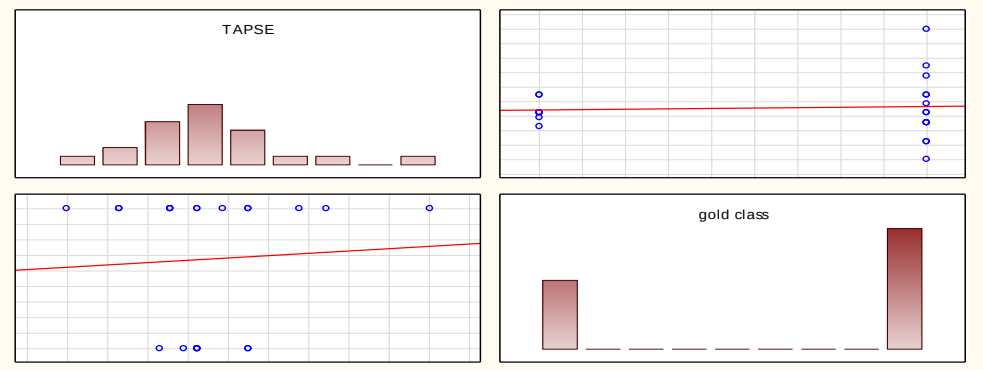
There was a weak positive rang correlation (Spearman rank order correlation) between RV basal and GOLD classification(r=0.146651).

Figure 5. Correlation between S TDV RV and GOLDclassification



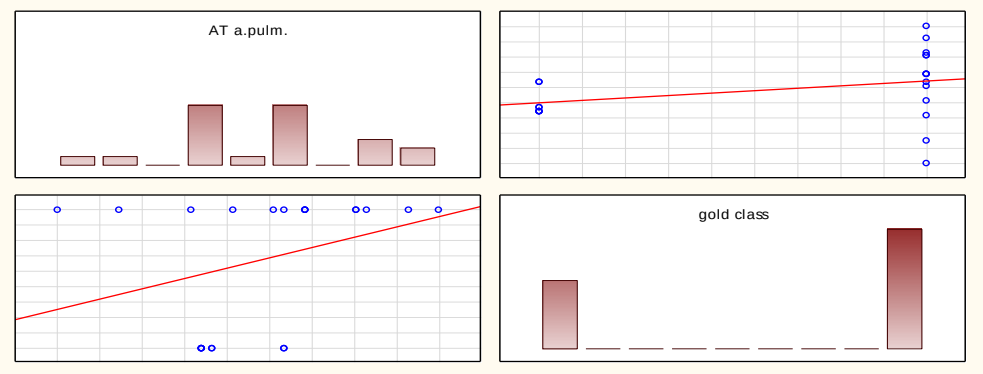
There was a weak rank correlation (Spearman rank order correlation) between S TDV RV and GOLDclassification.

Figure 6. Correlation between TAPSE and GOLD classification



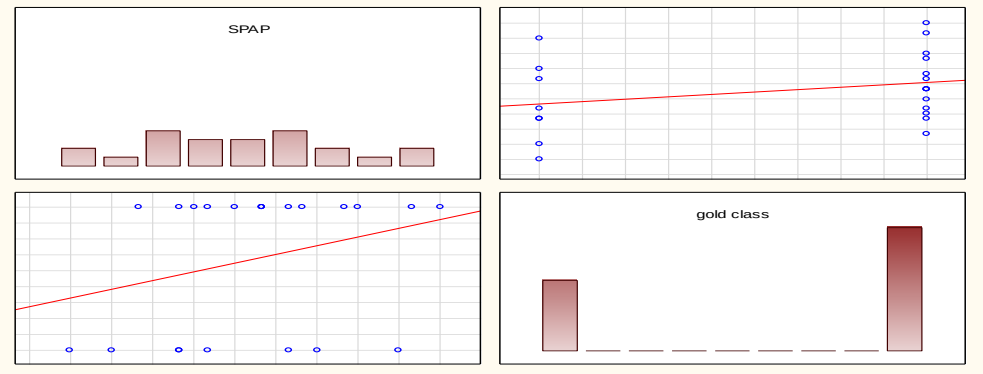
There was a positive weak rank correlation (Spearman rank order correlation) between TAPSE and GOLD classification (r=-0.015109).

Figure 7. Correlation between AT *a.pulm* and GOLD classification



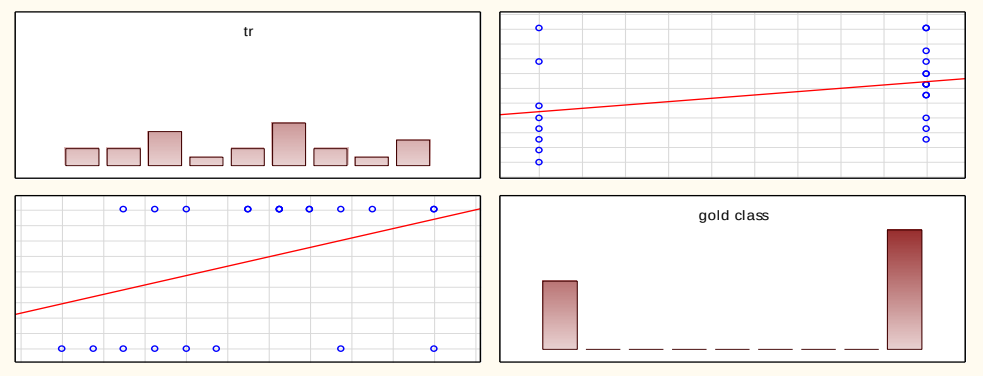
There was a positive moderate rank correlation (Spearman rank order correlation between AT *a.Pulm.* and GOLD classification(r.0.404425).

Figure 8. Correlation between SPAP and GOLD classification



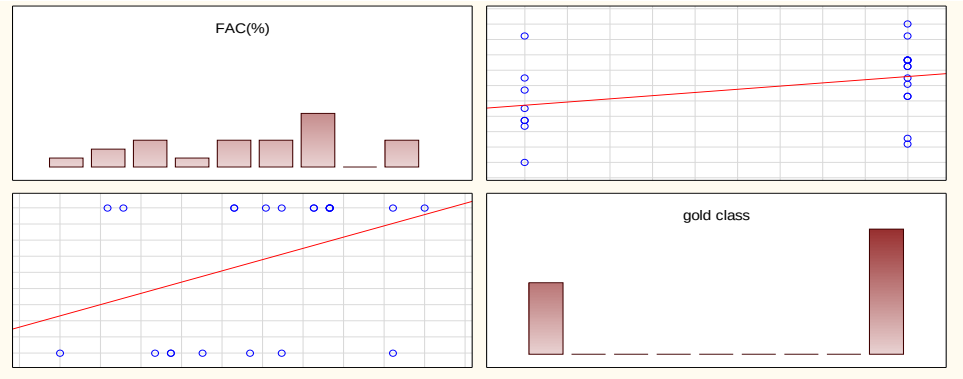
There was a positive moderate rank correlation (Sprearman rank order correlation) between SPAP and GOLD classification(r=0.283786).

Figure 9. Correlation between tricuspid regurgitation(m/sec) and GOLD classification



There was a positive moderate rank correlation (Spearman rank correlation) between tricuspid regurgitation m/sec and GOLD classification (r= 0.373828)

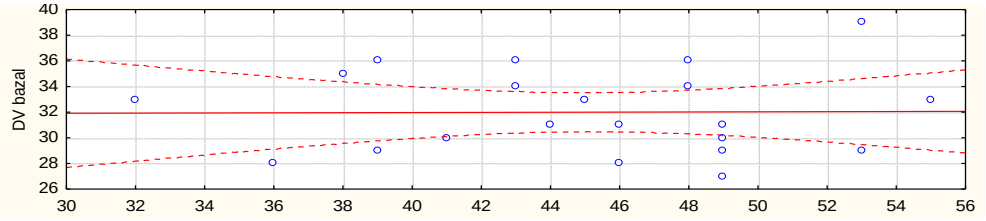
Figure 10. Correlation between FAC (%) and GOLD classification



There was a positive moderate rank correlation (Spearman rank order correlation) between FAC (%) and GOLD classification (r.0 388891)

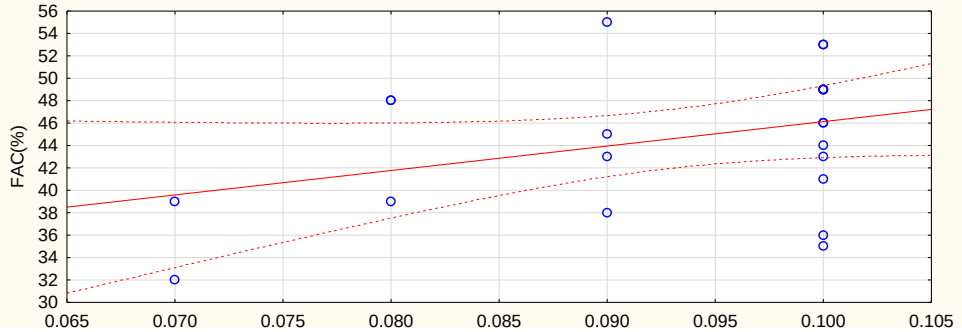
The analysis showed a weak positive correlation between echocardiographic parameters, right ventricle dimension, velocity of S wave of RV and TAPSE and the stage of the disease, but there was a moderate correlation between AT, sPAP and tricuspid regurgitation according to the stage of the disease, GOLD 3 and 4 classification.

Figure 11. Correlation between FAC (%) and RV basal dimension



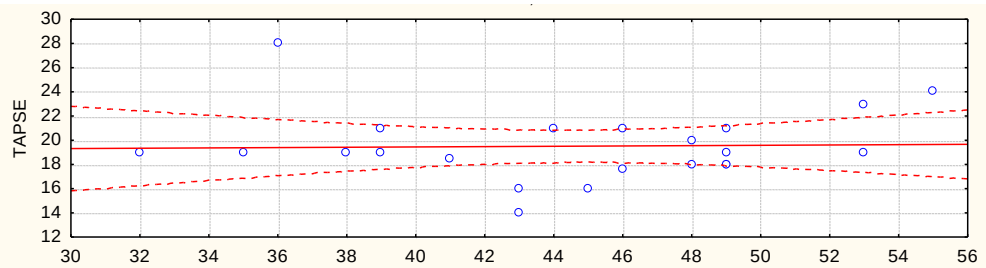
There was a weak correlation between FAC (%) and RV basal dimension(r=0.0103).

Figure 12. Correlation between FAC (%) and S TRV RV



There was a weak moderate correlation between FAC (%) and s TRV RV(r=0.363513).

Figure 13. Correlation between FAC (%) and TAPSE



There was a weak, negligible correlation between FAC (%) and TAPSE (r=0.0279).

The analysis showed a weak correlation between FAC as a parameter for global function of the right ventricle and the dimension of RV and TAPSE, but there was a moderate positive correlation between S wave of the tissue doppler as a parameter of the longitudinal function of RV.

Discussion

Early cardiovascular screening done by echocardiographic evaluation in patients with COPD, class 3 and 4 (defined by Gold) will contribute to defining the parameters that are important for monitoring the course of the disease, improvement and decrease of the frequency of hospitalization.

In our pilot study we made analysis of all the parameters,both demographic and echocardiographic,but the accent was put on the right heart parameters.

Male gender was prevalent (77.3%), and the average age was 66.4+6.3. In most of the studies male is a predominant gender as was the case in our study,too. This trend had tendency to decrease in later years of the observation period. One more scientific work published in 2019 in China. [7].

The right ventricle is necessary for obtaining the normal pump strength by the maintenance mechanism of normal perfusion in different pressure and loading conditions of the right ventricle [8].

The right ventricle mass is nearly 1/6 of the mass of the left ventricle due to physiological role of pumping in conditions with not so high pulmonary pressure. COPH results with different implications on the pulmonary artery pressure and different levels of right ventricular disfunction [9].

Wall movement of the right ventricle is complex and it is a result of shortening of the muscle fibres in three dimensions: circumferential, longitudinal and radial. During systole of the right ventricle there is a longitudinal shortening from the base to the apex and radial movement of the septum. Additionally, circumferential movement gives an opportunity for rotation and torsion of the right ventricle [8].

Echocardiography as a non-invasive and easy available method allows analysis of the morphology and function of the right ventricle, qualitative and guantitative. Estimation of RV is often hard to evaluate because of its complex anatomy, due to which the evaluation must be done in more echocardiographic windows and cross sections [8, 10].

In our study, the average values of diastolic dimension of the left ventricle expressed in mm was 41.6+3.0, ranging from 38 to 45 mm. The analysis showed that all patients had left ventricle dimension with low normal values, as well as the systolic and diastolic volumes of the left ventricle. Patients with severe /very severe degree of COPD have right ventricular overload that makes flattening of the interventricular septum which disables completely opening of the left ventricle. All that speaks in favor of small dimensions of the left heart cavities.

The feft ventricular systolic function expressed as ejection fraction (EF%) in all patients was above normal values, the average being 57.9+4.2, range from 53.0 to 68.0%. Despite the longevity and severity of the disease the pumping force for long time is with preserved ejection fraction EF%. In one meta-analysis that summarized the results from 15 studies in 2019 where primarily an estimation of the diastolic function was made, COPD patients were found to have normal EF% [11].

In our pilot study E/e' obtained by tissue doppler of the mitral valve showed an average value of 6.9+1.9,range 2.7 -11.9 m/sec. Normal values of diastolic function of the left ventricle was found in 18 patients (81.8%). The analysis of our data showed that most of the patients had normal diastolic function of the left ventricle, with weak correlation between diastolic function of LV and the severity of the disease. Two studies published these last years have different interpretations about diastolic dysfunction in patients with COPD. One study by a group of authors from Egypt published in 2016analyzed the correlation and the stage of diastolic dysfunction of LV in different groups of COPD.According to the severity of the disease, lower E/A ratio was found, extended deceleration time in patients with more severe form of COPD, but not all echocardiographic parameters for diastolic disfunction were analyzed. Reduction of E/E' ratio in patients with COPD is considered due to lower filling pressure of the left ventricle that is supported by the concept of reduced preload in patients with COPD. E/E' is a parameter that is independent of age, preload

and heart rate and itis an early marker for diastolic dysfunction [11, 12]. In one meta-analysis conducted in 2019(case control study) including patients with COPD and diastolic dysfunction was found that patients with COPD versus control group had increased E/E' ratio, lower E/A ratio and extended DT.

Our study showed that all 22 patients had normal TAPSE values (>16 mm). In 9 of the 22 patients, the value of S wave obtained from tissue doppler was below 0.09 cm/sec, that is, below the normal value. Having in mind the fact that these 2 parameters speak about assessment of longitudinal function of the right ventricle that are disturbed before global systolic function of RV, the estimation of longitudinal function of RV by tissue doppler was more sensitive than TAPSE determined by M-mode. In the literature, there are no studies on comparison of these two parameters and their sensitivity.

The parameter for defining global function of RV(FAC%) in our study had an average value of 44+6.2, and below cut-off value wasfound in two patients (9.1%). These two patients had increased SPAP in addition of development of pulmonary hypertension.

In Guptas *et al.* study from 2014, an analysis of 17 male patients with severe stage of COPD was made and all of them had neat global function of RV, FAC 56.8+10.6, average value of TAPSE was 27 mm and SPAP 35 mm/Hg. Basal diameter of RV was 35.194+9.184 mm. These results are similar to ours presented in this study [1].

Eight patients had a significant tricuspid regurgitation with values above 2.7 m/sec or 36.4%. This data indirectly gives us information about the degree of expression of pulmonary pressure and the development of pulmonary hypertension.

Expression of PAH in our pilot study was calculated based on the velocity of the tricuspid regurgitation, diameter and collapsibility of inferior vena cava as a marker for determining the pressure in the right atrium, placed in Bernoulli equation. An analysis of non-collapsibility of inferior vena cava in a patient with COPD is one of the parameters indicating an increased pressure in the right heart chambers. In the examined series in 50% of the patients non-collapse of vena cava more than 50% was registered [13].

A group of authors published a study showing enlarged dimensions of inferior venacava >20 mm and inspiratory collapse <50%, which were significantly associated with an increased mortality in patients with PAH [13].

In patients with significant pulmonary hypertension, the left ventricle dimensions in systole and diastole might be reduced as a result of septum deviation towards the left ventricle because of the right ventricle overload [13].

In our study the left ventricle dimensions were low- normal. A review paper published in 2009 demonstrated that pulmonary hypertension in most of the cases was mild to moderate in patients

with a severe form of COPD. A small sample of patients with COPD demonstrateda significant PAH and worse prognosis [14].

Pulmonary artery hypertension was often foundin COPD patients that were in an advanced stage of the disease, in approximately 20% of patients. Most of the cases were with mild to moderate form of pulmonary hypertension and 5% of them witha severe form. Patients with a severe form of COPD had an average survival of 40 months [14, 15].

Acceleration time (AT) at the level of the right ventricle outflow tract above valves of the pulmonary artery in the literaturehas been reported of no significance as is tricuspid regurgitation. In our study it was below 105 m/sec in all patients that might lead us to an increased pulmonary pressure, but still with no significance. Disadvantage of this parameter is that it has to be corrected if the heart rate is above >100/beats/min, that is 60-100 beats/min, but in our study there were no patients whose heart frequency was above 100/beats/min at the time of examination. The appearance of mid-systolic noch is associated with a significant PAH and right ventricular involvement, which was present in 2 of our patients [13].

Conculsion

Echocardiography as a noninvasive method with all its modalities has shown superiority in assessing and monitoring of patients with COPD. Echocardiography can give us in a fast and accurate waymany parameters in different stages of the disease, which will help in assessment and prognosis of patients with COPD.

The limitation of this study is the small number of patients in order to estimate many parameters, but this problem will be overcome with increasing the number of patients in the final study. According to the results obtained so far, we can conclude that echocardiography parameters for evaluation of the right and left ventricle remained within the reference limits long after the onset of the disease. Some of the echocardiographic parameters might be harbinger for initial deterioration of the right ventricle function and the development of pulmonary hypertension, such as tricuspid regurgitation, reduction of collapse of inferior vena cava, shortening of AT from tissue doppler of pulmonary valve, S wave from tissue doppler and many other parameters and derived parameters which in the final study will find their role.

References:

1. Gupta NK, Kumar Agrawal R, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. Lung India. 2001; 28(2): 105-9. doi:10.4103/0970-2113.80321
2. Raherison R, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009; 18(114): 213-21.doi: 10.1183/09059180.00003609
3. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. Int J Chron Obstruct Pulmon Dis. 2015; 10:95-109. doi: 10.2147/COPD.S54473
4. MeiLan KH, Dransfield MT, Martinez FJ.Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging.UpToDate.Available from: https://www.uptodate.com/contents/chronic-obstructive-pulmonary-disease-definition-clinical-manifestations-diagnosis-and-staging/print
5. Cao Z, Jia Y, Zhu B. BNP and NT-proBNP as Diagnostic Biomarkers for Cardiac Dysfunction in Both Clinical and Forensic Medicine. Int J Mol Sci. 2019; 20(8): 1820. doi: 10.3390/ijms20081820.
6. Putcha N, Bradley Drummond M, Wise RA, Hansel NN. Comorbidities and Chronic Obstructive Pulmonary Disease: Prevalence, Influence on Outcomes and Management. Semin Respir Crit Care Med. 2015; 36(4): 575–591. doi:10.1055/s-0035-1556063.
7. Zha Z, Leng R, Xu W, Bao H, Chen Y, Fang L, Liu Z, Dongqing Ye. Prevalence and risk factors of chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. BMC Pulm Med. 2019; 19:102. doi.org/10.1186/s12890-019-0864-0.
8. Bleeker GB, Steendijk P, Holman ER, Yu CM, Breithardt OA, Kaandorp TA, et al. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart 2006; 92 (Suppl 1): i19-26. doi: 10.1136/hrt.2005.082503
9. Lindqvist P, Calcutteea A, Michael Henein M. Echocardiography in the assessment of right heart function. Eur J Echocardiogr. 2008; 9: 225–34. doi:10.1016/j.euje.2007.04.002
10. Dutta T, Aronow WS. Echocardiographic evaluation of the right ventricle: Clinical implications.Clin Cardiol. 2017;40:542–8. https://doi.org/10.1002/clc.22694
11. Zhyvotovska A, Yusupov D, Kamran H, Al-Bermani T, Abdul R, Kumar S, et al. Diastolic Dysfunction in Patients with Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Case Controlled Studies. Int J Clin Res Trials. 2019; 4(2):137. doi:10.15344/2456-8007/2019/137
12. Eweda I, Hamada G. Concordance between Doppler and pulsed-wave Doppler tissue imaging in estimation of the degree of left ventricular dysfunction and correlating it to the degree of chronic obstructive pulmonary disease. J Saudi Hear Assoc 2016: 28:15-21. https://doi.org/10.1016/j.jsha.2015.04.001
13. Howard LS, Grapsa J, Dawson D, Bellamy M, Chambers JB, Masani ND, et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. Eur Respir Rev. 2012; 21:125:239–48.doi: 10.1183/09059180.00003912
14. Jyothula S, Safdar Z. Update on pulmonary hypertension complicating chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2009; 4:351-63. doi: 10.2147/copd.s5102
15. Das M, Tapadar SR, Mahapatra AB, Chowdhury SP, Basu S. Assessment of RV Function in Patients of COPD. J Clin Diagn Res. 2014: 8(3):11-3.doi: 10.7860/JCDR/2014/6440.4090

Трудот е лекториран од Ленче Даневска, професор по англиски јазик.

Л. Даневска, с. р.