



IMPORTANCE OF ELECTROCARDIOGRAPHIC EVALUATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Daniela Buklioska Ilievska, Nade Kochovska Kamchevska

Summary: *Introduction:* Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world and fourth leading cause after myocardial infarction, malignant diseases and cerebrovascular incidents. Patients with COPD are at increased risk of cardiovascular disease. Electrocardiography (ECG) carries valuable information about cardiac disease and prognosis.

Aim: To evaluate major ECG changes and their correlation to COPD severity.

Material and methods: Cross sectional study was conducted at 120 patients with COPD (age 40-75) and 60 subjects from general population without COPD, matched by age, gender and body mass index. All patients underwent resting ECG, 24 hour-ECG-Holter monitoring and pulmonary function tests.

Results: Abnormal ECG is more prevalent in COPD (83,33%) than in controls (26,67%). ECG findings in COPD: atrial fibrillation (AFF) (13,33%), tachycardia (36,67%), right axis deviation (23,33%), p-pulmonale (41,67%), right bundle branch block (15%), premature supraventricular (PSCs) and ventricular (PVCs) contractions (15%). ECG abnormalities due to right ventricular hypertrophy are increasing with COPD severity. Mean oxygen saturation in patients with tachycardia is lower than in those without (79,5%<92,9%). 24-hour-ECG-Holter monitoring allows detection of arrhythmias in asymptomatic patients and detected abnormalities were significantly higher compared to resting 12-lead-ECG. 24-hour-ECG-Holter results: PSCs (56,67%), paroxysmal supraventricular tachycardia (20%), PVCs (41,66%), PVC bigeminy (15%), ventricular couplets (10%), un-sustained ventricular tachycardia (5%), atrio-ventricular block of first degree (1,67%).

Conclusion: The prevalence of ECG abnormalities increases with COPD severity. Integrated-care approach for COPD patients is important for early detection of unrecognized coexisting cardiac disorders.

Keywords: COPD, ECG, right axis deviation, p pulmonale.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world and fourth leading cause after myocardial infarction, malignant diseases and cerebrovascular incidents (1,2). Patients with COPD are at increased risk of cardiovascular disease, anemia, polycythemia, malnutrition, muscular-skeletal disorder, osteoporosis, metabolic syndrome, diabetes, gastroesophageal reflux, anxiety, depression, hormonal disbalance, infections, lung carcinoma, thrombosis (3). Major cardiovascular disorders are: coronary artery disease, heart failure, cor pulmonale, pulmonary artery hypertension, arrhythmias, peripheral artery disease, carotid artery disease (4,5,6,7,8,9). Electrocardiography (ECG) carries valuable information about cardiac disease and prognosis. Electrocardiographic abnormalities are present in 75% of patients with COPD,

increasing in acute exacerbations and most frequent are supraventricular arrhythmias. Usually respond very well to medicaments (8,10,11). In literature there are several causes of the origin. Right-heart hypertrophy and/or dilatation as cause for supraventricular and metabolic disturbances because of chronic hypoxemia for ventricular premature beats (11). Lung hyperinflation leads to lower heart preload and cardiac output which is reason for tachycardia (12). COPD patient have autonomic dysfunction because of chronic hypoxia, rest tachycardia, increased risk for arrhythmias, conduction abnormality and ectopic beats (13). Multifocal atrial tachycardia (MAT) is frequent in COPD exacerbations and is accompanied with risk of death. Cardio-selective beta-blockers are safe treatment (13,14,15). The Copenhagen Heart Study at 13430 COPD patient published that risk for first episode of atrial fibrillation is 1,8 times higher in FEV1 (forced expiratory volume in 1st second) 60-



80% compared with $FEV_1 \geq 80\%$ (16). The Takahata Study from 2011, also showed that atrial fibrillation is higher in patients with $FEV_1 < 50\%$ (17). According to pulmonary treatment and the risk of arrhythmias, there are several notations. There is considerable concern that the use of pulmonary therapy increases morbidity and mortality in patients with COPD, although current meta-analyses have a conflict of interest. Lung Health Study has shown that ipratropium increases the risk of arrhythmia from placebo by 3.7 times (4). Salter and colleagues reported a meta-analysis of 18 randomized studies that examined the effect of long acting beta 2-agonists (LABA) and concluded that they increase the incidence of tachycardia and hypokalaemia leading to increased cardiovascular risk (11, 18). On the other hand, the UPLIFT study (Understanding Potential Long-Term Impacts on Function with Thiotropium) showed no increased risk of thiotropium use. The link between the use of beta 2-agonists as inhaled therapy in COPD and cardiovascular complications is still controversial. The study of TOWARDS a Revolution in COPD Health, in more than 6000 patients examined the effect of salmeterol, fluticasone propionate, a combination of salmeterol-fluticasone propionate or placebo, and found that cardiovascular risk in patients on salmeterol did not differ from the same in others groups (19). Theophylline gives an increased risk of tachyarrhythmias even at an undiminished serum concentration, with the highest frequency of atrial fibrillation (7).

AIM

1. To observe electrocardiographic changes and their dependence on spirometric parameters and findings from gas analysis;
2. To determine the correlation between different stages of COPD with the onset of cardiac rhythm and conduction disorders and which are most commonly reported;
3. To evaluate the correlation between the findings of gas analysis and risk of arrhythmias.

MATERIAL AND METHODS

Design: Cross sectional study.

Material: 120 patients with COPD (age 40-75) and 60 subjects from general population without

COPD, matched by age, gender and body mass index.

Inclusion criteria: Patients of both sexes, the current age of 40-80 years, with a pre-diagnosis of COPD in accordance with GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria for the diagnosis of COPD, cigarette smoking history ≥ 10 packs per year (pack-years), a signed consent for participation, a clinically stable condition at least 6 weeks prior to involvement;

Exclusion criteria: Age less than 40 years (why there is not enough time to act the risk factors responsible for the outbreak), more than 80 years (in the analysis of results bias may occur due to increased frequency of cardiac disease in age over 80 years as a result of fibrotic changes in the myocardium); obesity sleep apnea syndrome, patients with continuous oxygen therapy, asthma history, active tuberculosis, sarcoidosis, pulmonary carcinoma, pulmonary fibrosis, body mass index (BMI) $> 35 \text{ kg/m}^2$, diabetes mellitus; valvular heart disease; congenital heart disease, an electrocardiographic finding for left ventricular hypertrophy in a hypertensive heart disease; patients with contraindication for spirometry, electrolyte imbalance, hepatic; renal failure; anemia; muscular skeletal disease; patients with immunosuppressive therapy; patients who do not agree to participate.

Inclusion criteria for the control group: Age over 40 years, smoking history ≥ 10 pack-years, current or former smokers, without pulmonary abnormalities, spirometry with $FEV_1 > 80\%$ and $FEV_1 / FVC > 70\%$, stable clinical condition, without significant difference in sex, age, BMI and signed consent for participation.

Methods: All patients underwent resting ECG, 24 hour-ECG-Holter monitoring and pulmonary function tests.

1. Pulmonary investigation

* Assessment of the severity of dyspnea according to the Medical Research Council (MRC) Dyspnea Scale:

I degree - I feel hunger for air only with a strong effort;

II degree - I feel hunger for air when I rush flat or when I climb a mild uphill;



III degree - I go slower than people of the same age on flat because of difficulty breathing or I need to stop to get bored when I go to my room on a flat;

IV degree - I stop to go out after walking 100 meters or after a few minutes walking on a flat;

V degree - I breathe too hard to leave my home;

* Physical examination;

* Weight (W) and height (H) measurement in order to calculate Body Mass Index (BMI) according to the formula $W(kg) / H(m^2)$;

* Chest X-ray in two directions PA (posteroanterior) and LL (lateral) - in order to exclude respiratory disease other than COPD;

* Spirometry - measurement of FEV1 (forced expiratory volume in the first second) and FVC (forced vital capacity); A condition is the FEV1 / FVC ratio before the bronchodilator is given to be less than 0.7 (70%), for patients to be included in the study, to be diagnosed with COPD according to the GOLD criteria, and ratio should remain below 70% after the application of the bronchodilator; Spirometric measurements were performed according to the recommendations of the American Thoracic Society, using electronic Spirobank Spiromancer G USB Spirometer, after three pre-continental measurements, with a minimum of two having a difference of less than 5%.

* Bronchodilator test - It is performed in order to assess the reversibility of airway obstruction by inhaling bronchodilator beta 2 - agonist Salbutamol 4 puff = 400mg and after 30 minutes a control measurement of FEV1 was performed. If the reversibility of airflow was less than 15% then the patients were included in the study

* Gas analyzes in peace and after effort, performed by gas analyzer SIEMENS RAPIDPOINT 405. PaO2 (partial oxygen pressure), PaCO2 (partial carbon dioxide pressure), SaO2 (saturation with oxygen) were measured. Acid-base status - pH, BE - base excess, bicarbonate - HCO3, electrolyte - sodium, potassium, calcium (in order to exclude electrolyte abnormalities as a cause of arrhythmogenicity);

2. ECG evaluation

* Electrocardiography with 12 standard leads (paper speed 25mm/sec) after the patient's rest. The goal is to follow signs for: cor pulmonale: p-

pulmonale (p wave height ≥ 2.5 mm, signs of right ventricular hypertrophy - right axis, low QRS complex voltage, inversion of T wave in V1-V3, slow progression of R in V1-V6, R / S < 1 in V5V6, R / S > 1 in V1, R in V6 ≤ 5 mm, right bundle branch block; arrhythmias: supraventricular arrhythmias (atrial premature beats, atrial fibrillation-AFF, flutter or multifocal atrial tachycardia), A-V block, ventricular arrhythmias (ventricular premature beats, ventricular tachycardia);

* 24-hour Holter ECG monitoring (with Schiller ECG Holter Recorder);

RESULTS

Table 1. Spirometry results - prevalence of COPD in different stages

COPD severity	Investigated group N=120(%)
I: (FEV ₁ $\geq 80\%$ pred) - GOLD 1	6,66%
II: (FEV ₁ 50%-79% pred) - GOLD 2	35%
III: (FEV ₁ 30%-49% pred) - GOLD 3	36,67%
IV: (FEV ₁ $< 30\%$ pred) - GOLD 4	21,67%
Post-BD FEV ₁ / FVC % pred ($\leq 70\%$)	60,26 \pm 7,43
FEV 1 % pred \pm SD	47,52 \pm 17,92

Values in the control group - mean FEV1% before \pm SD - 99.28 \pm 14.71%, and the mean value of FEV1 / FVC% before \pm SD - 80.14 \pm 5.43%.

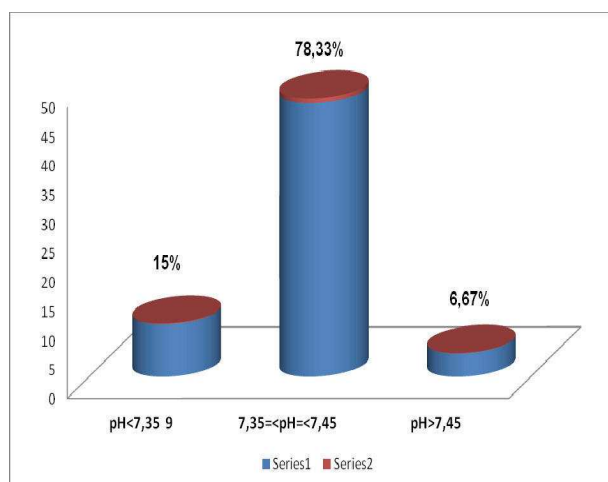


Image 1. Results from gas analysis in investigated group with COPD In respiratory acidosis pH < 7.35 were 15%



of total 120, and in respiratory alkalosis $pH > 7.45$,
6.67%.

HCO ₃ ⁻ - mean value	24,558 ± 4,218	23,043 ± 2,145
--	----------------	----------------

In the control group the mean PaO₂ value -
9.541 ± 1.011 kPa, PaCO₂ - 4.763 ± 0.712 kPa,
SaO₂% 91.468 ± 6.422%.

Correlation between partial oxygen pressure
(PaO₂ kPa) and spirometric values (FEV1% pred%)
using Pearson's correlation test (two-tailed) with
result ($r = 410$, $p = 0.001$) shows a significant
dependence ($p < 0.01$) between the two variables in
the positive direction, which means that there is a
linear dependence in the same direction (the
decrease in one value means the decrease on the
other).

Table 2. Gas analysis results in both groups

Parameters	Investigated Group N=120(%)	Controls N=60(%)
pH value - mean value	7,4110 ± 0,0582	7,405 ± 0,007
Base excess – mean value	3,380 ± 0,188	2,061 ± 0,964

Table 3. Correlation between PaO₂ (kPa) and FEV1% pred

Correlations

		FEV1%pred	PaO ₂ (kPa)
FEV1%pred	Pearson Correlation	1	,410**
	Sig. (2-tailed)		,001
	Sum of Squares and Cross-products	18944,983	648,053
	Covariance	321,101	10,984
	N	120	120
PaO ₂ (kPa)	Pearson Correlation	,410**	1
	Sig. (2-tailed)	,001	
	Sum of Squares and Cross-products	648,053	132,065
	Covariance	10,984	2,238
	N	120	120

**. Correlation is significant at the 0.01 level (2-tailed).

Table 3. Prevalence of resting-ECG changes in different stages of COPD

FEV1(%) pred	FEV1< 30 % pred GOLD IV	30%<=FEV1<50 % pred GOLD III	50%<=FEV1< 80% pred GOLD II	FEV1>80% pred GOLD I	FEV1 >80% pred
	Investigated Group (N=120)				Controls (N=60)
Normal ECG	1,67%	3,33%	8,33%	3,33%	76,67%
Atrial fibrillation (AFF)	1,67%	6,67%	0,00%	5,00%	6,67%
Heart rate >=100/min	16,67%	11,67%	8,33%	0,00%	16,67%
Right axis deviation	11,67%	8,33%	3,33%	0,00%	0,00%
Left axis deviation	3,33%	10,00%	6,67%	0,00%	10,00%
p-pulmonale	13,33%	21,67%	8,33%	0,00%	6,67%
RBBB (Right Bundle Branch Block)	5,00%	3,33%	5,00%	1,67%	3,33%
R/S < 1 in V5V6	5,00%	8,33%	0,00%	0,00%	0,00%
R/S > 1 in V1	5,00%	3,33%	5,00%	1,67%	0,00%



Slow R- progression V1-V6	10,00%	11,67%	8,33%	0,00%	0,00%
Low QRS complex (<5mm) in D1	1,67%	1,67%	3,33%	0,00%	3,33%
Supraventricular premature beats (SVPc)	6,67%	6,67%	0,00%	3,33%	6,67%
Ventricular premature beats (VPc)	1,67%	5,00%	6,67%	0,00%	3,33%

The median value of oxygen saturation in subjects with tachycardia was lower than in subjects without tachycardia (79.4977 <92.8789).

Holter monitoring allows the observation of cardiac rhythm and arrhythmia detection in asymptomatic patients. The analysis was done with the Schiller ECG Holter Recorder within 24 hours. The most commonly detected arrhythmia was supraventricular premature beats - 56.67%, supraventricular tachycardia in 20%, individual ventricular premature beats in 41.66%, atrial fibrillation in 15% (in one patient transient AFF), transient unstained ventricular tachycardia (un-sustained-VT) in three patients (5%) and a transient AV block of first degree in one patient (1.67%).

Table 2. Prevalence of Holter-monitoring-ECG changes in COPD

	% of Investigated
Supraventricular premature beats (SVPc)	56,67%
Supraventricular tachycardia (SVT)	20%
Ventricular premature beats (monomorphic) - VPc	41,66%
Ventricular premature beats (polymorphic)	11,67%
Ventricular bigeminy	15%
Ventricular couplets	10%
Transient un-sustained-VT	5%
Atrial fibrillation	15%
Transient first degree AV-block	1,67%

Fatal arrhythmias: VES couplets, un-sustained VT were noted in 13.33%, and the mean age in these patients was 64.25 years. In all patients with fatal arrhythmias, QTc interval was greater than 440ms. Correlation between pH value and the risk of fatal arrhythmias recorded with 24-hour-Holter-monitoring using Chi-Square test showed that patients with pH value lower than 7.35 have a higher risk of fatal outcome ($p < 0.001$).

DISCUSSION

In our study a comparison was made between electrocardiographic findings in patients with COPD and without COPD, which showed that ECG abnormalities were more prevalent in COPD. Atrial

fibrillation (AFF) was 13.33%, tachycardia 36.67%, right axis 23.33%, p-pulmonale 41.67%, RBBB 15%, SVPc 16.67%, VPc at 15%. In contrast to the examined ECG, the control group was in the normal range in 73.33%, the normal axis had 90%, leftward axis 10%, right bundle branch block 3, 33%. Tachycardia had 16.67%, AFF 6.67%. Electrocardiographic changes for right heart hypertrophy (right-ward axis deviation, right bundle branch block, deep S in V6) are correlated with spirometric parameters proportional with increasing in airflow limitation. Similar findings have been published in the literature by Warnier, Holtzman, Finkelstein with their collaborators and other large studies, which have shown an increased incidence of arrhythmias in these patients, particularly atrial fibrillation (15,20,21). Similar to other studies, we have shown that tachycardia increases with GOLD stage (20,22,23). Holter monitoring is a much more sensitive method that allows more detailed analysis of electrocardiographic changes in patients with COPD, observing the cardiac rhythm continuously for 24 hours, indicating abnormalities that were absent on a routine electrocardiographic record in rest. Detected arrhythmias in the investigated group: SVPc in 56.67%, SVT in 20%, monomorphic VPc - 41.66%, single polymorphic VPc - 67%, ventricular bigeminy in 15%, ventricular couplets in 10%, AFF in 15% (in two patients transient AFF), transient unstained ventricular tachycardia (un-sustained-VT) in six patients (5%) and transient AV block of first degree in two patients (1.67%). Fatal arrhythmias: VES couplets, non-sustained VT were noted in 13.33%, and the mean age in these patients was 64.25 years. All patients with fatal arrhythmias QTc interval with a value greater than 440ms. The findings are comparable to the values obtained by Dabadghao VS and co-workers, where SVPc is 50%, VPc at 32%, AFF at 14%, there is a higher frequency of fatal arrhythmias ventricular couplets in 30% and unsupported ventricular tachycardia in 22% (24). Findings in Konecny and associates are with a slightly higher frequency of atrial fibrillation of 23.3%, and unsupported ventricular tachycardia at 13%. In our study, as with Dabadghao VS and co-



workers, there was no statistical significance between the association of arrhythmias with the weight of COPD (24). Comparison of pH and risk for fatal outcome of patients according to results detected at 24 - hour Holter monitoring showed high statistical significance (using Chi - Square test, $p < 0.001$), which means respiratory acidosis in global respiratory failure is a significant risk factor for arrhythmias (11).

CONCLUSIONS

1. Correlation between partial oxygen pressure (PaO₂ kPa) and spirometric values (FEV₁% pred) shows significant dependence ($p < 0.01$) between the two variables in the positive direction, there is a linear dependence in the same direction.
2. Electrocardiographic changes are correlated with spirometric parameters proportional to the severity of COPD;
3. Correlation between the occurrence of tachycardia and SaO₂ (%) showed that there is a statistically significant difference in the prevalence of oxygen saturation values in subjects with tachycardia and prevalence of oxygen saturation values in subjects without tachycardia.
4. There was no significant dependence on the occurrence of different types of arrhythmias and FEV₁% pred.
5. Global respiratory failure is associated with an increased frequency of cardiac arrhythmias, and respiratory acidosis is a significant risk factor for malignant rhythm disorders.
6. ECG is inexpensive and easily accessible screening method with an informative and diagnostic character for pulmonary disease, which should be routinely performed in all patients with COPD.
7. 24-hour ECG - Holter monitoring is much more sensitive in the detection of cardiac arrhythmias than resting-ECG;

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Executive Summary: Global Strategy for Diagnosis, Management, and Prevention of COPD - Updated 2018.
2. Marie M. Budev, DO, MPH, Alejandro C. Arroliga, MD, Herbert P. Wiedemann, MD, and Richard A. Matthay, MD. Cor Pulmonale: An Overview. *Semin Respir Crit Care Med*. 2003;24(3):233-44.
3. Anthony S. Fauci A, Braunwald E, et al. Principles of Harrison's Internal Medicine. 17th Ed. New York: McGraw-Hill, 2008; pp. 1635-1642.
4. Don DS, Man P. Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease. *Can J Physiol Pharmacol* 2005;83(1):8-13.
5. Sabit R, Bolton C, et al. Sub-clinical left and right ventricular dysfunction in patients with COPD. *Respiratory medicine*. 2010; 104(8):1171-1178.
6. Lucas-Ramos P, Izquierdo-Alonso J, Rodriguez-Gonzalez J, Fernandez Frances J, Lozano P, Bellón-Cano J. Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study). *International Journal of COPD*. 2012;7 679-686.
7. Jeremy A, Kadiev S, Criner G, Scharf S, Minai O, Diaz P. Cardiac disease in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc*. 2008; 5(4):543-548.
8. Hunninghake D. Cardiovascular Disease in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc*. 2005; 2:44-49.
9. Finkelstein J, Cha E, Scharf S. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *International Journal of COPD*. 2009; 4:337 - 349.
10. Harrigan RA, Jones K. ABC of clinical electrocardiography. Conditions affecting the right side of heart. *BMJ*. 2002;324:1201-1204.
11. Cardiac arrhythmia in patients with chronic obstructive pulmonary diseases. *DocGuide.com. Pulmonology*. 2005
12. Criner GJ. COPD and the heart: when less lung means more heart. *Chest* 2010; 138(1):6-8.
13. Jeremy A, Kadiev S, Criner G, Scharf S, Minai O, Diaz P. Cardiac disease in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc*. 2008; 5(4):543-548.
14. Hunninghake D. Cardiovascular Disease in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc*. 2005; 2:44-49.
15. Finkelstein J, Cha E, Scharf S. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *International Journal of COPD*. 2009; 4:337 - 349.
16. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J*. 2003;21(6):1012-6.
17. Shibata Y, Watanabe T, Osaka D, Abe S, Inoue S, Tokairin Y, Igarashi A, Yamauchi K, Kimura T, Kishi H, Aida Y, Nunomiya K, Nemoto T, Sato M,



- Konta T, Kawata S, Kato T, Kayama T, Kubota I. Impairment of Pulmonary Function is an Independent Risk Factor for Atrial Fibrillation: The Takahata Study. *Int J Med Sci*. 2011; 8(7):514-522.
18. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: A meta-analysis. *Chest* 2004; 125(6):2309–2321.
19. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-789.
20. Warnier MJ, Rutten FH, Numans ME, Kors JA, Tan HL, de Boer A, Hoes AW, De Bruin ML. Electrocardiographic characteristics of patients with chronic obstructive pulmonary disease. *COPD*. 2013 Feb;10(1):62-71.
21. Holtzman D, Aronow WS, Mellana WM, Sharma M, Mehta N, Lim J, et al. Electrocardiographic abnormalities in patients with severe versus mild or moderate chronic obstructive pulmonary disease followed in an academic outpatient pulmonary clinic. *Ann Noninvas Electrocardiol* 2011; 16(1):30–32.
22. Gunduz H, Talay F, Arinc H, Ozyildirim S, Akdemir R, Yolcu M, et al. Heart rate variability and heart rate turbulence in patients with chronic obstructive pulmonary disease. *Cardiol J* 2009; 16(6):553–559.
23. Volterrani M, Scalvini S, Mazzuero G, Lanfranchi P, Colombo R, Clark AL, et al. Decreased heart rate variability in patients with chronic obstructive pulmonary disease. *Chest* 1994; 106(5):1432–1437.
24. Dabadghao VS et al. A clinical study of cardiac rhythm disturbance in patients with chronic obstructive pulmonary disease using 24 hour Holter monitoring. *International Journal of Research in Medical Sciences (Int J Res Med Sci)*. 2016 Mar;4(3):701-705.

Daniela Buklioska Ilievska
Adress: „Nikola Parapunov” 31/1-3 Skopje, Macedonia
Tel: 00389 70304066
e-mail: dbuklioska@yahoo.com