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Assessment of Endothelial Dysfunction by Measuring Von Willebrand Factor and Exhaled Nitric Oxide in Patients with Chronic Obstructive Pulmonary Disease

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A B S T R A C T

Chronic obstructive pulmonary disease (COPD) is a multisystemic disease, one of the leading causes of mortality and morbidity. The aim of this research is to assess the level of markers of endothelial dysfunction, vWf and the exhaled nitric oxide (NO) depending on the severity of COPD. The study included 100 subjects: 60 patients with COPD without adjoining cardiovascular comorbidity, and 40 patients as the controls. The subjects underwent a fractional exhaled nitric oxide test (FeNO), spirometric testing, and diffusing capacity of the lung for carbon monoxide test (DLCO), samples were taken of their vein blood to analyze the level of vWf (using the vWf:RCO method), C-reactive protein (CRP), fibrinogen, cholesterol, triglycerides as well as the acid base status. COPD patients then filled COPD assessment test (CAT test) and the modified dyspnea scale (mMRC). The results showed that in patient group that higher levels of vWf are associated with lower values of exhaled NO, which means that higher levels of vWf are associated with lower values of exhaled NO. By comparing the ill subjects from four groups (A, B, C and D), a difference was established between the level of vWf [F (3.56 =0.24; p=0.869], while, although statistically not significant, the highest level of exhaled NO was found in group A and the lowest in group D. The rise in the value of vWf is followed by the rise of fibrinogen values, which is another marker of endothelial dysfunction. The results of this research have shown that a systemic inflammation and hypoxia in the early stages of COPD, when no significant changes in the absolute values of FEV1 are present, stipulate the existence of endothelial dysfunction together with the clinically relevant differences in the levels of vWf and exhaled NO.

***Key words**: COPD, endothelial dysfunction, nitric oxide, von Willenbrand factor, fibrinogen*

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex multisystem disease and a leading cause of mortality and morbidity. Systemic inflammation, which is a consequence of smoking, leads to endothelial damage and a subsequent reduction in vasodilator capacity (which results in endothelial dysfunction), and initiates the atherosclerotic process. COPD represents an independent risk factor for cardiovascular disease.[1–3] The main mechanisms in the development of endothelial dysfunction in patients with COPD are systemic inflammation, hypoxia, oxidative stress, and sympathetic activation[4]. Endothelial dysfunction is a syndrome with multisystemic effects and is marked by inappropriate endothelial activation or loss of vasodilator, antithrombotic, and anti-inflammatory capabilities. Dysfunctional endothelium is also characterized by the increased expression of adhesion molecules, chemokines, and other cytokines, which play an important role in the initial stage of the atherosclerotic process.

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Methods that are now used to assess the endothelial dysfunction include invasive methods that measure coronary diameter and flow and noninvasive methods such as the high-resolution ultrasound test flow-mediated dilation of peripheral artery disease (which is considered the »gold standard« in the diagnosis of endothelial dysfunction)[5]. Many studies have confirmed that among the noninvasive methods of assessing endothelial dysfunction is detecting the presence of von Willebrand factor (vWf)[6]. vWf is a multimeric glycoprotein synthesized primarily in endothelial cells. The level of vWF, reflects general endothelial functional disorder as well as the level of activity of the atherosclerotic process[5]. The level of vWf has been assessed in a series of clinical conditions. The main advantage of vWF is its availability of detection. Previous studies confirm that the level of vWF is positively correlated with the level of oxidative stress, which plays a role in the development of the atherosclerotic process[7,8]. Endothelial dysfunction is associated with the reduced bioavailability of nitric oxide (NO) because of its reduced production by endothelial cells and/or because of increased inactivation of NO synthase by reactive oxygen species, which occurs in numerous inflammatory conditions[5,9,10].

Previous studies evaluating the level of NO in the breath of patients with COPD have shown that the level of NO is correlated with the general condition of the patient and the level of the post-bronchodilator forced expiratory volume in 1 second (FEV1)[11–14]. The use of inhaled corticosteroids or bronchodilators does not affect the NO level[15–17]. Research results have confirmed the interdependence of NO and vWf levels in the development of the atherosclerotic process and confirmed that the reduced production of NO results in increased levels of vWF, which partially blocks the action of NO synthase[14,18]. Different research methods have confirmed endothelial dysfunction in patients with COPD[19–21] and that the plasma concentrations of markers of endothelial dysfunction increase significantly with each exacerbation of COPD, independent of concomitant cardiovascular comorbidity[22–25].This study aims to determine whether the level of vWf increases as the level of exhaled NO decreases in patients with increasing severity of COPD[26], and to determine whether there are differences between patients with and without elevated cholesterol and triglyceride levels. The assessment of endothelial dysfunction in patients with COPD is extremely important clinically and for determining the appropriate treatment for the multisystem consequences of COPD.

Materials and Methods

The study included 100 subjects: 60 patients with COPD, who were treated at the Department of Pulmonary Diseases at the Department of Internal Medicine at the University Hospital Osijek (Osijek, Croatia) and 40 controls (20 healthy smokers with normal lung function and 20 nonsmokers) in the period of May 2012. to June 2013. The patients and controls were over 18 years. Patients who had acute exacerbation of COPD, malignant diseases, radiological signs of pulmonary hypertension, asthma, chronic renal failure, or patients who were regularly taking angiotensin-converting enzyme inhibitor blockers, angiotensin receptor blocker statins, oral corticosteroids, or hypoglycemic agents were excluded from the study. The participants were previously familiar with the investigation and provided signed informed consent. The study was approved by the Ethics Committee of the University Hospital Osijek (Osijek, Croatia) and conducted according to the principles of the Helsinki Declaration. A case history was obtained from all study participants in regard to hypertension, diabetes, duration and amount of smoking, coronary heart disease, stroke, peripheral artery disease. They also underwent a physical examination. Their body height and weight were measured. Based on these data, each study participant's body mass index (BMI) was calculated.

Respondents underwent standardized noninvasive measurement of fractional exhaled NO (ppb), spirometric testing, and measurement of the diffusing capacity of the lung for carbon monoxide (DLCO). Venous blood samples were collected from each subject for the noninvasive analysis of the levels of vWF, C-reactive protein (CRP, reference range <0.5 mg/L), fibrinogen (reference range 1.8–3.5 g/L), cholesterol (reference range <5.00 mmol/L), and triglycerides (reference range <1.70 mmol/L). A sample of arterial blood was obtained for the analysis of each subject's acid-base status. Laboratory determination of the vWf level (reference range 0.50–1.50 L) was obtained by the von Willebrand-ristocetin cofactor test (vWF:RCO), which measures platelet agglutination in plasma in the presence of ristocetin. The ristocetin-induced agglutination rate is correlated with the concentration and the functional activity of plasma vWF. Ristocetin binds to vWF on Glu1239-Pro-Gly Gly1242. Participants who had COPD completed the following questionnaires: COPD assessment test (CAT) and the modified dyspnea scale (mMRC). These participants were divided into 4 groups based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[26] or based on the results of spirometry, the risk of exacerbations, and the presence of symptoms (as assessed by the questionnaires) (Table 1).

Statistical analysis

The collected data were analyzed by the statistical program SPSS for Windows, version 19 (IBM, New York, United States) before the processing of data. The Shapiro-Wilk normality test was used to determine the distribution of the numerical variables. We used *t*-tests to compare 2 independent groups and analysis of variance (ANOVA) and analysis of covariance (ANCOVA) to compare 2 or more independent groups. ANCOVA is different from the well-known and more frequently used ANOVA, in that it allows for controlling the effects of certain variables. The sample size required for this study was determined by using the calculated required sample size (G*Power 3 Germany).

TABLE 1
COMBINED ASSESSMENT OF COPD

Patient	Characteristics	Spirometric Classification	Exacerbration per year	mMRC	CAT
A	Low risk Less symptoms	GOLD 1-2	<1	0–1	<10
B	Low risk More symptoms	GOLD 1-2	<1	≥2	≥10
C	High risk Less symptoms	GOLD 3-4	≥2	0–1	<10
D	High risk More symptoms	GOLD 3-4	≥2	≥2	≥10

mMRC – Modiefied British Research Coucinl breathlessness scale, CAT – COPD Assessment test, GOLD – Global initiative for chronic Obstructive Lung Disease

Results

Data were collected for one hundred subjects aged 34 to 79 ($\overline{X}$=54.64; SD=11.70). The participants were divided into two groups: 1) the patient group (n=60) and 2) the control group (N=40). The control group was divided into two subgroups, namely A) smokers (n=20) and B) nonsmokers (N=20). The age range in the patient group from 42 to 79 years and the average age is M=60.67 years (SD=9.28). The age range of the control group of smokers goes from 35 to 65 years with an average age being $\overline{X}$ = 44.79 years (SD=9.00). The average age of the control group of nonsmokers is $\overline{X}$=45.47 (SD=7.91 years; the age range is 34–60 years). According to the GOLD guidelines (the 2011 classification), with reference to the spirometry findings, the risk of exacerbations and the presence of symptoms which are assessed by the adequate questionnaire, the patients were divided into 4 groups. While doing so, twenty of them were categorized into group A, 26 into group B and 7 patients into groups C and D.

By comparing the participants from the four groups (A, B, C and D) the difference in the level of vWf [F (3.56)=0.24; p=0.869] and the level of exhaled NO [F (3.56)=1.45; p=0.239] was determined. The highest level of exhaled NO was found among the participants from group A, and the lowest among the patients from group D (Table 2).

A comparison of the four patients groups (i.e., A, B, C and D) showed that there was no significant difference in the level of vWF [F (3.56)=0.24; p=.869] or the level of exhaled NO [F (3.56)=1.45; p=0.239]. The difference was not statistically significant (Table 2); however, the participants in group A had the highest level of exhaled NO and the participants in group D had the lowest level of exhaled NO. Within the group of the patients and the control group of nonsmokers the higher readings of vWf are associated with the lower reading of exhaled NO (Figure 1). Furthermore, it was established in all three

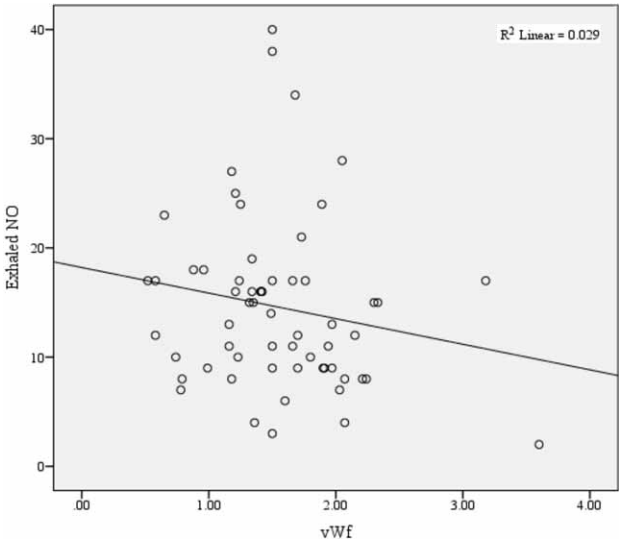

Fig. 1. Relationship between levels of vWf and exhaled NO in the group of patients.

TABLE 2
DESCRIPTIVE STATISTICS FOR VWF AND EXHALED NO IN PARTICIPANTS WITH VARYING SEVERITY OF COPD

	Patient	N	$\overline{X}$	SD	Minimum	Maximum
vWf(L)	A (low risk, less symptoms)	20	1.62	0.57	0.52	3.18
	B (low risk, more symptoms)	26	1.51	0.59	0.74	3.60
	C (high risk, less symptoms)	7	1.54	0.65	0.58	2.30
	D (high risk, more symptoms)	7	1.43	0.48	0.58	2.07
Exhaled NO (ppb)	A (low risk, less symptoms)	20	16.35	8.26	4	40
	B (low risk, more symptoms)	26	15.19	8.81	2	38
	C (high risk, less symptoms)	7	11.43	4.42	6	17
	D (high risk, more symptoms)	7	10.43	2.14	8	14

N – number of patient, vWf – von Willenbrand factor, NO – nitric oxide

participant groups that with the increase of the vWf value, the value of fibrinogen level also increases (Table 3).

As shown in Tables 3–3b, from all the other tested markers in all three groups it was, as expected, established that lower values of pO_2 are followed by higher values of vWf. In the patient group was found that the increase of vWf values is followed by decreased BMI values (Table 3). In the same group it was established that the increase of pack/years (the number of cigarettes smoked in a day) x (years of smoking)/20, is followed by a lower vWf value, but if only current smokers are taken from the patient group, higher vWf values are connected to more smoked cigarettes and more years of smoking (r=

TABLE 3
INTERCORRELATIONS AMONG THE TESTED MARKERS IN THE THREE GROUP OF PATIENT

Patient (N=60)	2	3	4	5	6	7	8	9	10	11	12	13	14
1. vWf	–0.17	0.30*	0.30*	–0.05	0.16	0.10	0.04	0.33*	–0.07	0.09	0.22	–0.29*	–0.29*
2. Exhaled NO	—	–0.12	–0.17	–0.03	–0.10	0.17	0.18	0.08	–0.11	–0.06	–0.04	0.02	0.04
3. Fibronogen		—	0.53†	–0.03	–0.04	–0.09	–0.07	–0.13	–0.14	–0.08	0.05	0.01	–0.17
4. CRP			—	–0.20	0.13	–0.17	–0.01	0.04	–0.11	–0.01	0.15	–0.04	–0.07
5. Cholesterol				—	0.30*	0.28*	0.18	0.19	0.11	0.15	0.08	0.32*	0.02
6.Tryglicerides					—	0.17	0.25	0.27*	–0.10	0.04	–0.05	0.26*	–0.11
7. FEV1						—	0.68†	0.47†	–0.08	–0.18	–0.11	–0.03	–0.07
8. FEV1/FVC							—	0.41†	–0.06	–0.06	–0.01	0.14	–0.14
9. DLCO								—	–0.04	–0.06	–0.09	0.26*	–0.27*
10. pO_2									—	0.03	–0.06	–0.17	–0.14
11. pCO_2										—	0.82†	–0.04	–0.02
12. HCO_3^-											—	–0.10	–0.11
13.BMI												—	0.10
14. pack/years													—

*p<0.05, †p<0.01, ‡p<0.001, FEV1 – post-bronchodilator forced expiratory volume in 1 second, FEV1/FVC – post-bronchodilator forced expiratory volume in 1 second/forced vital capacity, DLCO – diffusing capacity of lung for carbon monoxide, pO_2 – partial pressure of oxygen, pCO_2 – partial pressure of carbon dioxide, HCO_3^- – bicarbonate, BMI – body mass index

TABLE 3a
INTERCORRELATIONS AMONG THE TESTED MARKERS IN THE GROUP OF CONTROL SMOKERS

Control smokers (N=20)	2	3	4	5	6	7	8	9	10	11	12	13	14
1. vWf	0.09	0.19	0.19	0.08	0.17	–0.18	–0.15	–0.46*	–0.11	–0.44	–0.34	–0.25	0.13
2. Exhaled NO	—	0.61†	0.72†	0.11	–0.15	–0.04	–0.06	0.11	–0.88†	–0.05	–0.20	0.20	0.56*
3. Fibronogen		—	0.49*	–0.31	–0.49*	0.14	–0.11	–0.05	–0.64†	0.15	–0.12	0.16	0.17
4. CRP			—	0.09	–0.10	0.00	–0.01	0.18	–0.82†	0.23	–0.04	0.29	0.20
5. Cholesterol				—	0.81†	0.18	0.36	0.51*	–0.11	–0.16	–0.08	0.43	0.27
6.Tryglicerides					—	0.03	0.30	0.43	0.19	–0.30	–0.18	0.44	0.05
7. FEV1						—	0.31	0.57*	0.08	0.08	0.01	0.26	–0.34
8. FEV1/FVC							—	0.47*	0.15	–0.24	–0.18	0.36	0.01
9. DLCO								—	–0.01	0.09	0.03	0.54*	–0.14
10. pO_2									—	–0.01	0.21	–0.16	–0.52*
11. pCO_2										—	0.80†	–0.10	–0.34
12. HCO_3^-											—	–0.26	–0.31
13. BMI												—	0.30
14. pack/years													—

*p<0.05, †p<0.01, ‡p<0.001, FEV1 – post-bronchodilator forced expiratory volume in 1 second, FEV1/FVC – post-bronchodilator forced expiratory volume in 1 second/forced vital capacity, DLCO – diffusing capacity of lung for carbon monoxide, pO_2 – partial pressure of oxygen, pCO_2 – partial pressure of carbon dioxide, HCO_3^- – bicarbonate, BMI – body mass index

TABLE 3b
INTERCORRELATIONS AMONG THE TESTED MARKERS IN THE GROUP OF CONTROL NON- SMOKERS

Control non-smokers (N=20)	2	3	4	5	6	7	8	9	10	11	12	13	14
1. vWf	–0.25	0.56*	–0.01	0.26	0.15	–0.18	0.24	0.24	–0.23	0.04	0.06	0.12	–0.08
2. Exhaled NO	—	–0.08	0.08	–0.24	0.12	0.15	–0.19	–0.18	–0.09	0.20	0.11	0.05	–0.22
3. Fibronogen		—	0.52*	–0.08	0.42	0.24	–0.21	–0.05	–0.49*	–0.03	–0.33	0.26	0.03
4. CRP			—	0.06	0.75†	–0.06	–0.13	0.11	–0.36	–0.40	–0.62†	0.42	–0.21
5. Cholesterol				—	0.15	–0.30	0.26	0.13	0.29	–0.37	–0.32	0.44	0.17
6.Tryglicerides					—	–0.27	–0.07	0.17	–0.37	–0.38	–0.47*	0.24	–0.12
7. FEV1						—	–0.03	0.16	0.23	–0.13	–0.32	–0.03	–0.06
8. FEV1/FVC							—	0.57*	0.43	–0.45	–0.18	0.04	–0.21
9. DLCO								—	–0.44	–0.27	–0.47*	–0.10	–0.44
10. pO_2									—	–0.44	–0.27	–0.47*	–0.10
11. pCO_2										—	0.85†	0.01	0.05
12. HCO_3^-											—	–0.15	0.09
13. BMI												—	–0.05
14. pack/years													—

*p<0.05, †p<0.01,‡ p<0.001, FEV1 – post-bronchodilator forced expiratory volume in 1 second, FEV1/FVC – post-bronchodilator forced expiratory volume in 1 second/forced vital capacity, DLCO – diffusing capacity of lung for carbon monoxide, pO_2 – partial pressure of oxygen, pCO_2 – partial pressure of carbon dioxide, HCO_3^- – bicarbonate, BMI – body mass index

0.06; p=0.781), just as with the control group of smokers (Table 3a). By using T-test for independent samples it was found that the average value of pack/years was significantly larger among the patients ($\overline{X}$=37.80; SD=33.90) than among the control group of smokers ($\overline{X}$=16.10; SD=10.36). As can be seen in Table 4, after the age control, as expected, a significant difference between the three groups was found regarding the level of exhaled NO, spirometry findings, diffusion capacity and the partial oxygen pressure. For each significant difference, the magnitude of the effect of the difference was calculated. As can be seen in Table 4, the magnitude of the difference for exhaled NO and pO_2 is moderate (according to Cohen's border values), and for DLCO, FEV1 and FEV1/FVC it is great. Practically, it means that the differences between the groups considering the values of individual markers are not just statistically, but also clinically significant, in other words, relevant.

By using the statistical analysis it was found that within the group of ill participants, 42 of them (70%) had elevated cholesterol, and 18 of them (30%) had elevated triglycerides. In the control group of smokers a similar percentage (63.2%) had elevated cholesterol, and one third (31.6%) also had elevated triglycerides, whereas in the nonsmokers' group as much as 71.85% of them had elevated cholesterol, and around one third (31.2%) had elevated triglycerides. By using T-test for independent samples, no differences were found in vWF [t (96)=0.20; p=0.841] and fibrinogen values [t (96)=1.31; p=0.193] for those participants with higher levels of cholesterol and triglycerides compared to the other participants. The comparison of the patients undergoing different types of therapy regarding the usage of inhalational corticosteroids established that, from the entire number of patients, 47 of them were receiving treatment with inhalational corticosteroids. By using T-test for independent samples, a difference was established between the two participant groups regarding the values of exhaled NO, t (57)=2.23; p=0.032, in which process among the ill ones who had inhalational corticosteroid in their therapy, a lower value of exhaled NO was measured ($\overline{X}$=13.45; SD=6.84) than within the participants who weren't receiving the aforementioned therapy ($\overline{X}$=18.92; SD=10.43). By using the same test no difference was found between the two participant groups regarding the vWf values t(57)=1.29; p=0.203, although higher vWf values were noticed in the group which received a therapy without the inhalational corticosteroids than within the group which received therapy with inhalational corticosteroid ($\overline{X}$=1.50; SD=0.62). Finally, by processing it was established that a longer period of treatment (expressed in months) was followed by higher vWf values (r=17; p=0.198).

Discussion

This research, in accordance with the previous researches, has confirmed the existence of endothelial dysfunction in patients with COPD using as markers the level of serum vWf and the exhaled NO,[23–26] with the emphasis that, unlike with the majority of previous researches, the ill ones didn't have associated cardiovascular comorbidity. By excluding one of the most important factors that affects endothelial dysfunction, and including only the ill ones in a stable stage of the disease, the research had the goal to, as precisely as possible, and as

TABLE 4
COMPARISON OF THE THREE GROUPS OF PARTICIPANTS WITH REGARD TO SEROLOGICAL MARKERS

Marker	Group	$\overline{X}$	SD	Compare group (F ration)	η_p^2	Post-hoc (Games-Howell)
vWf	Patient	1.54	0.57	2.58	0.05	
	Control smokers	1.48	0.83			
	Control non-smokers	1.08	0.45			
Exhaled NO	Patient	14.58	7.86	4.19*	0.08	P<CS
	Control smokers	19.42	13.85			
	Control non-smokers	13.00	6.11			
Fibronogen	Patient	4.19	1.13	0.38	0.01	
	Control smokers	3.35	1.22			
	Control non-smokers	3.19	0.96			
CRP	Patient	5.64	6.54	0.33	0.01	
	Control smokers	2.48	3.22			
	Control non-smokers	2.82	2.69			
Cholesterol	Patient	5.50	1.01	1.01	0.02	
	Control smokers	5.80	1.73			
	Control non-smokers	5.72	1.03			
Tryglicerides	Patient	1.41	0.71	0.08	0.01	
	Control smokers	1.70	1.06			
	Control non-smokers	1.61	1.12			
FEV1	Patient	65.13	18.69	54.05†	0.54	P<CS, P<CNS††
	Control smokers	105.51	13.75			
	Control non-smokers	115.62	10.91			
FEV1/FVC	Patient	57.65	9.01	37.97†	0.45	P<CS, P<CNS
	Control smokers	80.90	7.45			
	Control non-smokers	85.70	13.49			
DLCO	Patient	57.58	21.84	19.52†	0.29	P<CS, P<CNS
	Control smokers	78.71	12.13			
	Control non-smokers	93.70	12.00			
pO_2	Patient	9.69	1.37	3.69*	0.07	CS<CNS
	Control smokers	10.68	3.87			
	Control non-smokers	12.23	1.33			
pCO_2	Patient	5.26	0.54	0.12	0.01	
	Control smokers	5.17	0.41			
	Control non-smokers	5.25	0.62			
HCO_3^-	Patient	25.56	2.12	0.15	0.01	
	Control smokers	25.15	1.37			
	Control non-smokers	25.48	2.18			

η_p^2 – mesure of efect size, vWf – von Willenbrand factor, *p<0.05, P – patient, CS – control smokers, FEV1 – post-bronchodilator forced expiratory volume in 1 second, †p<0.001, CNS – control non-smokers, FEV1/FVC – post-bronchodilator forced expiratory volume in 1 second/forced vital capacity, DLCO – diffusing capacity of lung for carbon monoxide, pO_2 – partial pressure of oxygen, pCO_2 – partial pressure of carbon dioxide, HCO_3^- – bicarbonate

realistically, assess the systemic effects of COPD. Due to the high percentage of associated cardiovascular comorbidity (14–62% of COPD patients) which increases with the progress of COPD, the research is limited to an isolated population of patients with COPD which explains the sample size in this study[27]. In this research fibrinogen was used as a control marker of endothelial dysfunction, whose values correlate positively with vWf, and the level of exhaled NO is decreased by the growth of the aforementioned two markers. These results are consistent with previous findings showing that endothelial dysfunction is associated with the reduced activity of NO synthase, which is simultaneously blocked by the increase in vWF levels[22]. Taking into account the severity

of COPD (GOLD's guidelines, the 2013 classification), it is necessary to emphasize that most patients, according to the seriousness of the disease, belong to groups A and B because with the advancement of the disease, the presence of comorbidities which independently of COPD affect the endothelial dysfunction is more significant, whereas the level of exhaled NO was, in accordance with the assumptions, the lowest in group D; in other words, it decreased with the increase of the severity of COPD.

As expected, with a longer period of treatment, there is a progression in endothelial dysfunction, which is confirmed by the data about positive correlation between the length of the treatment and the vWf level.

When discussing the current smoking status, the control group of smokers, as well as the current smokers in the ill-group, had higher values of exhaled NO in comparison to the rest of the patients because active smoking transitorily increases the oxidative stress in the airways, which results in an increase in exhaled NO[28,29]. The results obtained in this research have shown that the application of inhalation corticosteroids with the patients with COPD leads to a decrease in NO level[30], which can be explained by the fact that their application increases as the severity of the disease enhances (according to GOLD's guidelines), thus resulting in, as we mentioned earlier, decreasing the level of exhaled NO.

Taking into account BMI, the vWF value was elevated in patients with lower BMI values which stems from the fact that the loss of body weight is the result of increased levels of inflammatory markers and hormonal changes, which presents a negative survival predictor. In doing so it confirms the fact that the range of the entire inflammatory process itself is responsible for the development of endothelial dysfunction.

The results of this research have shown that the systemic inflammation, hypoxia in the early stages of COPD when there are no significant changes in the absolute values and FEV1, are responsible for clinically relevant, although not statistical, considerable increase in endothelial dysfunction markers. These results can be explained by the small sample size, but it has to be emphasized that the sample size is the result of the fact that only about 10% of those with COPD are without adjoining comorbidity and are not taking medications which influence the interpretation of the endothelial dysfunction's markers. The advantage of these two markers of endothelial dysfunction compared with the others is their clinical availability. Future researches should determine how to apply aforementioned markers of endothelial dysfunction in everyday clinical practice, in the treatment of COPD and in monitoring the systemic consequences of COPD.

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PROCJENA ENDOTELNE DISFUNKCIJE NA TEMELJU VON WILLENBRANDOVA FAKTORA I IZDISAJNOG DUŠIKOVA OKSIDA KOD OBOLJELIH OD KRONIČNE OPSTRUKTIVNE PLUĆNE BOLESTI

S A Ž E T A K

Kronična opstruktivna plućna bolest (KOPB) je multisistemska bolest, jedan od vodećih uzroka mortaliteta i morbiditeta. Cilj ovog istraživanja je procjenti razinu markera endotelne disfunkcije vWf I izdisajnog dušikova oksida (NO) ovisno o stupnju težine KOPB-a.U istraživanje je uključeno ukupno 100 ispitanika, 60 oboljelih od KOPB-a bez pridruženog kardiovaskularnog komorbiditeta, a 40 ispitanika su kontrolne skupine. Ispitanici su učinili FeNO test, spirometrijskog testiranja, mjerenje difuzijskog kapaciteta za CO, uzeti su im uzorci venske krvi za analizu razine vWf (metodom vWF:RCO), C-reaktivni protein (CRP), fibrinogena, kolesterola, triglicerida, te analiza acido-baznog statusa. Oboljeli od KOPB-a potom su ispunili odgovarajuće upitnike COPD assessment test (CAT test) and the modified dyspnea scale (mMRC). Rezultati su pokazali da u skupini oboljelih odnos između vWf i izdisajnog NO je negativan što znači da su više vrijednosti vWf povezane s nižim vrijednostima FeNO. Usporedbom oboljelih iz četiri skupine (A, B, C i D) utvrđena razlika u razini vWf [F (3,56)=0,24, p=0,869], dok iako ne statistički značajna, najviša razina izdisajnog NO utvrđena u skupini A, a najniža u skupini D. Porast vrijednosti vWf praćen je porastom vrijednosti fibrinogena, još jednog markera endotelne disfunkcije. Rezultati ovog istraživanja su pokazali da sistemska upala i hipoksija već u početnim stadijima KOPB-a kad nisu prisutne značajne promjene u apsolutnim vrijednostima FEV1 uvjetuju postojanje endotelne disfunkcije uz klinički relavantne razlike u razini vWf i izdisajnog NO.