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DYNAMICS OF CHARACTERISTICS OF RESPIRATORY FUNCTION FOR THE DEVELOPMENT OF CORONARY HEART DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE

Abstract

Chronic obstructive pulmonary disease (COPD), along with cardiovascular disease, belongs to the leading chronic non-infectious diseases of our time, which, occurring in comorbidity, lead to the development of severe complications, which aggravate each other. **Objective:** to determine the methods of diagnosis and prevention of coronary events in patients with COPD living in the northern latitudes based on the dynamic assessment of the parameters of respiratory function. **Materials and methods**. During five years, extended instrumental examination (body plethysmography, echocardiography) was provided in 182 patients with COPD (mean age 65.0±1.2 years) within the study. Coronary events during prospective follow-up were recorded in 66 patients (mean age 65.0±1.2 years). **Results:** in a cohort of 976 patients with COPD, the number of patients with moderate bronchial obstruction (54 %) was 6 times higher than the number of patients with severe bronchial obstruction (8.6 %) ($p<0.001$). During the five-year progression of impairments of volume and speed parameters of respiratory function was registered period in patients with isolated COPD (n=116). It should be noted that the course of COPD in this sample of patients was associated with a predominant decrease in restrictive function parameters, and manifested in the form of a decrease in the expiratory reserve volume (ERV) by 20.6 % ($p=0.004$). In patients with COPD, constituting a risk group for the development of coronary events, there was no significant dynamics of respiratory function parameters for five years ($p>0.05$). Patients with lower values of volume parameters of respiratory function, such as ERV and inspiratory capacity (IC), showed a recorded coronary event during the five-year follow-up period ($p<0.05$). The greatest number of coronary events among patients of moderate and high risk with COPD was recorded in the first 3 years of follow-up, among patients of very high risk — evenly over 5 years. Coronary events were associated with periods of exacerbation of the underlying disease ($p<0.05$). Their incidence rate (myocardial infarction, angina, and coronary death) for five years in patients with COPD with very high, high and moderate coronary risk was 33.9 %, 10.5 %, 1.52 %, respectively. Using stepwise discriminant analysis, it was found that the leading prognostic markers of coronary events in patients with COPD living in the northern latitudes are the data of echocardiography (end-diastolic dimension of the left ventricle, pulmonary artery systolic pressure) and body plethysmography (ERV). **Conclusion.** Body plethysmography and echocardiography must be provided in all patients with COPD to identify silent restrictive respiratory function disorders at the first stage of the disease. Given the low level of diagnosis of COPD in Russia, a long asymptomatic course of the disease, and the development of COPD after 10 years of living in the North, according to the literature, it is recommended to conduct an annual body plethysmography as a screening method of examination of all smokers living in the northern latitudes. Thus, the use of body plethysmography with a targeted assessment of volume parameters, as well as echocardiography, allows to identify groups of patients at risk of coronary events and, thereby, to carry out timely prevention of the latter among patients with COPD.

Key words: *chronic obstructive pulmonary disease, respiratory function, ischemic heart disease, comorbidity*

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IC — inspiratory capacity, IHD — ischemic heart disease, EDD_{LV} — left ventricular end-diastolic dimension, MEFR — maximum expiratory flow rate, FEV_1 — forced expiratory volume in 1 second, ERV — expiratory reserve volume, PASP — pulmonary artery systolic pressure, HF — heart failure, CVDs — cardiovascular diseases, COPD — chronic obstructive pulmonary disease, ECG — electrocardiogram

Chronic obstructive pulmonary disease (COPD) is one of the leading chronic non-contagious diseases. It has been established that the primary cause of death among the patients with COPD is not only respiratory failure but also cardiovascular diseases (CVDs) that are very widespread in the world today as well [1, 2, 3]. Patients suffering from COPD are at 2 to 3 times higher risk of cardiovascular mortality [4]. In the northern regions this risk is 5 to 6 times higher [5] and contributes approximately 50 % of the total number of deaths [4]. According to Kerry Schnell et al., comorbidity with underlying COPD is the rule rather than the exception, since 96.4 % of patients with COPD aged 45 and older have at least one concomitant disease [6]. Findings of studies conducted by domestic and foreign therapists and pulmonologists show that 85 % of patients with COPD have essential hypertension involving target organs, 64 % — coronary atherosclerosis; 19 % — a past history of ischemic stroke; 21 % — confirmed thromboembolism of pulmonary arteries; 39 % — excess fat deposits, etc. [7]. The main types of CVDs in case of COPD, according to Correia L. et al., include ischemic heart disease (IHD), hypertension and heart failure (HF). According to European researchers, the incidence of COPD and IHD in patients of older age groups is 62 %; the mortality rate in case of comorbidity of the two conditions exceeds 50 %. Patients with newly diagnosed COPD have 5.5 times higher incidence rate of myocardial infarction as compared to the general population, and 3 times higher incidence rate of CVA [3, 8].

In view of some shared components of pathogenesis, particular features of a clinical picture form in cardiorespiratory comorbidity accompanied with mutual aggravation syndrome [9]. According to modern views, great importance for the development and progression of COPD and CVDs is attached to the disruption of the functioning of the cellular component of immune system, phagocyte and cytokine systems. Due to hemodynamic stress, free-radical oxidation, systemic inflammation and imbalance in the proteinases–inhibitors system, patients with COPD show early formation of endothelial dysfunction, change in collagen and elastin metabolism in vascular walls, damage to cellular and molecular structures, activation of procoagulant and growth factors in a vessel wall, which lead to its destructuration and fibrosis [10, 11]. Owing to hypertrophy and hyperplasia of endothelium and subendothelium in response to hypoxia developed over time, intima and media thickening occurs in the vascular wall, which results in the disruption of its functional activity, progression of hypertrophy and hyperplasia of smooth muscle cells, an increase in the content of collagen and elastin [12]. Endothelium dysfunction and vascular remodeling worsen steadily even in the stable course of COPD, contributing to development and progression of a coronary disease. Progressive hypoxemia aggravates COPD as well as comorbid CVDs.

Numerous studies show the relationship between the decrease in the forced expiratory volume in 1 second (FEV_1) and increased development of IHD [13–22]. In patients with mild and moderate COPD, the risk of cardiovascular mortality increases by 28 % with every 10 % of decrease in FEV_1 [2, 18]. It has been established that the primary factors, which determine changes in FEV_1 in patients with COPD during long-term follow-up include smoking status, frequency of exacerbations, appropriate therapy and therapeutic compliance [23–25, 27]. When selecting an approach for management of patients with COPD and cardiac comorbidity, there is need to bear in mind the cumulative risk of potential complications, especially for the elderly [2, 21, 22].

The search for effective methods to prevent and treat conditions with a multimorbidity/comorbidity is one of the most critical medical and social challenges due to the increase in life expectancy

of the population and the number of patients with comorbidities. Early diagnosis of IHD in COPD patients remains relevant. However, it is complicated due to the similarity of the symptoms, low diagnostic value of routine electrocardiogram (ECG) examination, peculiarities of clinical signs when one disease leaves another in "the shadow" [22–24, 26].

Thus, early diagnosis and prevention of cardiovascular diseases in COPD through the search for the most informative risk factors for their development remain relevant. The identification of such risk factors should be referred to predictive medicine, which is one of components of the modern 5P model of medicine.

Study objective: to identify methods for diagnosing and preventing coronary events in patients with COPD, who live in northern latitudes, based on dynamic assessment of respiratory function parameters.

Materials and Methods

Over a five-year period of observation, 976 patients with COPD (mean age: 60.7±0.35 years) were treated at the Surgut Hospital. The ratio of male to female patients was 5:1, n=820 (84 %) and n=156 (16 %), respectively. The mean age of the patients was comparable (females — 61.1±0.94 years, males — 60.7±0.37 years) (p=0.671).

The inclusion criterion was the presence of confirmed COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD, 2011, 2014). Exclusion criteria were IHD confirmed at the beginning of the study, other concomitant respiratory diseases, cancer and hematologic diseases, end-stage kidney or liver failure, chronic heart failure of 3 and 4 NYHA classes, and diabetes mellitus types 1 and 2.

From among 976 patients, of which 19 patients (2 %) reached the fatal endpoint (coronary death) [25], 182 patients were randomized to undergo extended instrumental examination for five years. Duration of COPD was 8.6±0.23 years. Duration of living in northern regions was 29.9±0.5 years. In the course of prospective observation of the group, changes in the key morphofunctional parameters of respiratory and cardiovascular systems were assessed. As a result, predictors of coronary events were identified. Non-fatal events including acute (myocardial infarction) and chronic forms of IHD (angina, silent myocardial ischemia, cardiac rhythm disorder, heart failure) newly diagnosed in patients during the observation period were reported in 66 patients (control group) of 182 (mean age: 65.0±1.2 years) (60 males (mean age: 63.0±1.1 years) and 6 females (mean age: 74.0±0.8 years) (p<0.01)). It is worth noting that no fatal coronary events were reported in the control group. The treatment group included 116 patients (at the ratio of 5:1: 96 males (mean age: 60.9±1.2 years) and 20 females (mean age: 54.9±2.7 years) (p=0.140)). It should be noted that during the prospective observation of over 182 patients, the development of coronary events (IHD), in particular, was assessed. The clinical diagnosis of IHD in the course of dynamic observation was confirmed based on the generally accepted diagnostic standards using the appropriate laboratory and instrumental examination, according to the International Classification of Diseases, 10th Edition, as well as based on the criteria of the WHO Expert Committee and the Russian Society of Cardiology guidelines (2006, 2007, 2008, 2011).

The main study methods included: the interview method (recording of complaints, medical history), physical examination (measuring of blood pressure (BP), identifying leading clinical syndromes of COPD and IHD), laboratory tests (complete blood count, biochemical analysis), instrumental examination methods (body plethysmography, echocardiography performed as per standard methods). Coronary risk was identified in all patients at the baseline as per the Systematic Coronary Risk Evaluation (SCORE), taking into account gender, age, systolic blood pressure, total cholesterol, and smoking status. A relative risk score was applied to young persons. The term coronary risk was used, first of all, with consideration for the exact translation of the SCORE title; and second, due to the fact that the assessment covered the incidence of coronary events and peculiarities of coronary disease course with underlying COPD. According to the European Guidelines on cardiovascular disease prevention in clinical practice, all the patients were divided into groups at moderate (up to 5 % as per the SCORE), high (5–9 % as per the SCORE), and extremely high (over 10 % as per the SCORE) risk.

Statistics were processed using Microsoft Excel 2007, IBM SPSS Statistics 22. The Student's *t*-test was used for inter-group differences (the data distribution equality was assessed by the Kolmogorov-Smirnov test), and the Pearson's c^2-test and *z*-test were applied in the analysis. Coronary events over the observation period were recorded by the Kaplan-Meier analysis. The latter were predicted using stepwise discriminant analysis. The expiratory reserve volume was taken as a grouping factor.

Results and Discussion

In the cohort of 976 patients with COPD, the number of patients with moderate bronchial obstruction (54 %) was 6 times as much as those with extremely severe one (8.6 %) (p<0.001). The least proportion of patients had mild bronchial obstruction (4.2 %) (p<0.001). One in three study patients had severe COPD (33.2 %) (p=0.004). Among females, patients with moderate bronchial obstruction prevailed (71.8 %), as compared to males (50.7 %) (p=0.014). Severe COPD was predominant among males (36.1 %) in contrast to female with COPD, among whom this severity was reported only in one in five cases (18.0 %) (p=0.005) (Table 1).

The average annual incidence of exacerbations that require hospitalization in COPD patients was 1.6±0.1. Females experienced exacerbations rarer (1.3±0.1) than males (1.6±0.1) (p=0.046), which is associated with less pronounced bronchial obstruction. So, the average annual number of exacerbations in severe and extremely severe COPD was 1.8±0.0 and 1.8±0.0, respectively, which was much greater than in mild COPD, i. e., 1.2±0.0 (p<0.001). The worsening of bronchial obstruction and exacerbations of COPD result in the development and progression of cardiovascular diseases [2, 26, 27]. Moderate bronchial obstruction among the study patients was reported in one in two patients in the treatment group (54 %, n=62) and the control group (50 %, n=33) (p>0.05)). Extremely severe bronchial obstruction was reported rarer (8.6 %, n=10 (treatment group); 7.3 %, n=5 (control group) (p>0.05)) (p<0.001). Mild severity was observed in the least number of patients (4.2 %, n=5) (treatment group); 3.8 %, n=3) (control group) (p>0.05). Severe bronchial obstruction was reported in one in three patients (33.2 %, n=39 (treatment group); 38.9 %, n=25 (control group)) (p>0.05).

When analyzing expiratory function parameters in COPD patients without any reported coronary event over the five-year period of observation (n=116), it was established that FEV_1 was decreased in males with COPD by 30.0%, and in females — by 26 %, indicating the severity of bronchial obstruction in this patient population. Females showed greater inspiratory capacity (IC) (%) (p=0.050). Tiffeneau index in males decreased by 9.5 %, and in females — by 4.6 %. Analysis of characteristics of

Table 1. *Bronchial obstruction in patients with COPD (n = 976)*

Parameter	All patients n=976 abs. (%)	Male n=820 abs. (%)	Female n=156 abs. (%)	p	χ^2
	1	2	3		
I (FEV_1 >70 %)	40 (4.2 %)	32 (4.0 %)	8 (5.1 %)	p_{1-2}=0.935 p_{1-3}=0.724 p_{2-3}=0.647	χ^2_{1-2}=0.007 χ^2_{1-3}=0.125 χ^2_{2-3}=0.209
II (FEV_1 70–50 %)	528 (54.0 %)	416 (50.7 %)	112 (71.8 %)	p_{1-2}=0.451 **p_{1-3}=0.042** **p_{2-3}=0.014**	χ^2_{1-2}=0.569 **χ^2_{1-3}=4.120** **χ^2_{2-3}=6.044**
III (FEV_1 50–30 %)	324 (33.2 %)	74 (36.1 %)	28 (18 %)	**p_{1-2}<0.001** **p_{1-3}=0.005** **p_{2-3}=0.005**	**χ^2_{1-2}=97.722** **χ^2_{1-3}=7.864** **χ^2_{2-3}=7.788**
IV (FEV_1 <30 %)	84* (8.6 %)	19* (9.2 %)	8* (5.1 %)	**p_{1-2}<0.001** p_{1-3}=0.233 p_{2-3}=0.104	**χ^2_{1-2}=28.153** χ^2_{1-3}=1.483 χ^2_{2-3}=2.649

Note: the significance of differences between patients with COPD by the χ^2 test

patency of respiratory tract at different levels identified no differences between males and females. The maximum expiratory flow rate $(MEFR)_{25}$ was reduced in males by 46.7 %, and in females — by 65.6 % (p=0.063); $MEFR_{50}$ was decreased in males by 59.4 %, and in females — by 51.5 % (p=0.633).

Among 66 COPD patients with IHD diagnosed during the observation period, mixed respiratory function impairments with predominant obstructive changes were found (Table 2).

At the beginning of the study, only several volumetric lung parameters were different between the COPD patients and those with COPD and confirmed IHD. So, the minimum values of ERV, IC and PEFR were found in males with COPD with reported coronary events (p<0.05).

Over the five-year period, the worsening of respiratory function impairments concerning its volumetric and velocity parameters was reported in patients suffering from COPD only (n=116). It should be noted that the progress of COPD in this number of patients was associated primarily with the reduction in restrictive parameters presented as ERV decrease by 20.6 % (p=0.004) (Figure 1).

Table 2. *Respiratory function in patients with COPD and IHD at the beginning of the study (M±m) (n=66)*

Parameter (unit)	COPD and IHD Male n=60	COPD and IHD Female n=6	U	p
Vital Capacity (VC_{max}) (%)	76.44±2.50	74.11±7.56	168	p>0.05
Forced VC (%)	73.20±2.51	71.30±12.80	180	p>0.05
FEV_1 (%)	47.93±2.52	57.14±14.91	171	p>0.05
Tiffeneau index (%)	61.16±2.15	51.47±3.78	126	p>0.05
$MEFR_{25}$ (%)	20.79±1.28	16.43±0.01	54	p>0.05
$MEFR_{50}$ (%)	45.5±5.6	43.2±3.1	52	p>0.05
Inspiratory capacity (%)	78.33±3.95	115.69±24.24	**90**	**p<0.05**
Expiratory reserve volume (%)	59.43±4.32	70.24±7.74	**92**	**p<0.05**
Peak expiratory flow rate (%)	43.96±2.48	46.95±6.15	**135**	**p<0.05**

Note: p — the reliability of differences in performance between patients with COPD and IHD of male and female is determined by the U-test

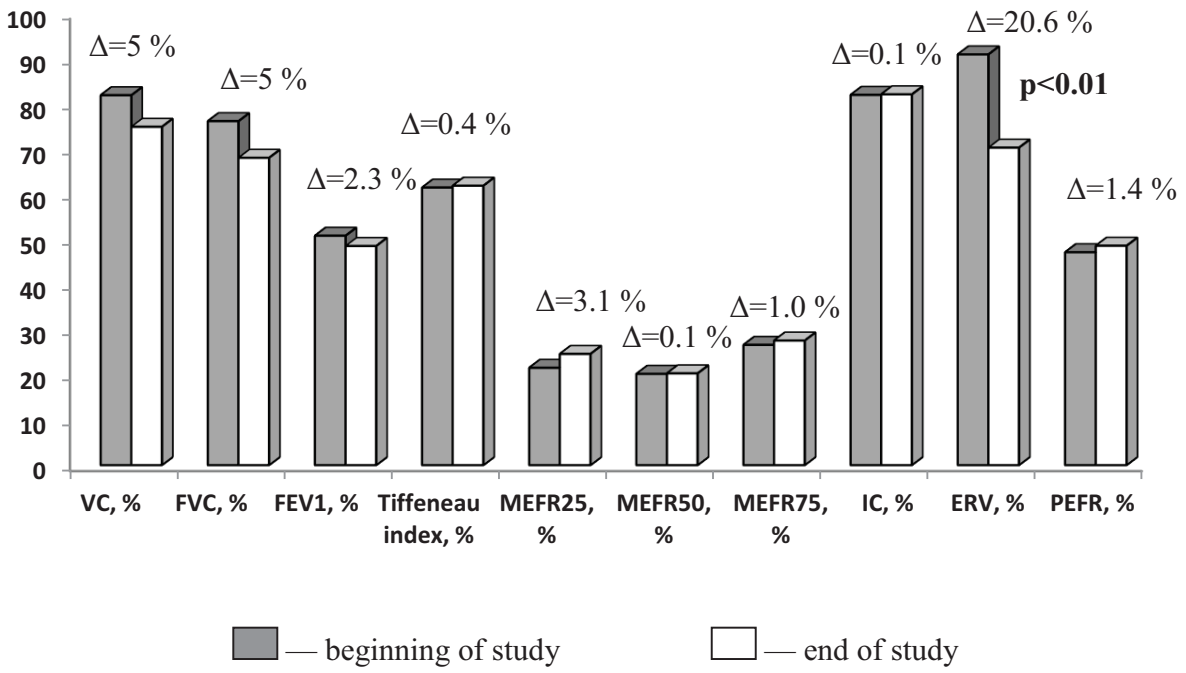

Figure 1. *Dynamics of respiratory function parameters in patients with chronic obstructive pulmonary disease (n=116)*

Table 3. *Five-year dynamics of main parameters of respiration function in patients with COPD and IHD (M±m) (n=66)*

Index (unit)	COPD and IHD (beginning of the study) n=66	COPD and IHD (end of the study) n=66	W	ρ
VC_{max} (%)	78.14±2.86	76.44±2.50	–0.502	0.616
FVC (%)	73.02±2.93	73.20±2.51	–0.275	0.783
FEV_1 (%)	47.72±2.76	47.93±2.52	–0.590	0.555
Tiffeneau Index (%)	58.60±2.24	57.88±2.09	–0.543	0.587
Inspiratory capacity (%)	80.15±3.92	78.33±3.95	–0.465	0.642

Note: ρ — the reliability of differences in patients with COPD and IHD at the beginning of the study and after 5 years was determined by the W-criterion. The differences are not significant

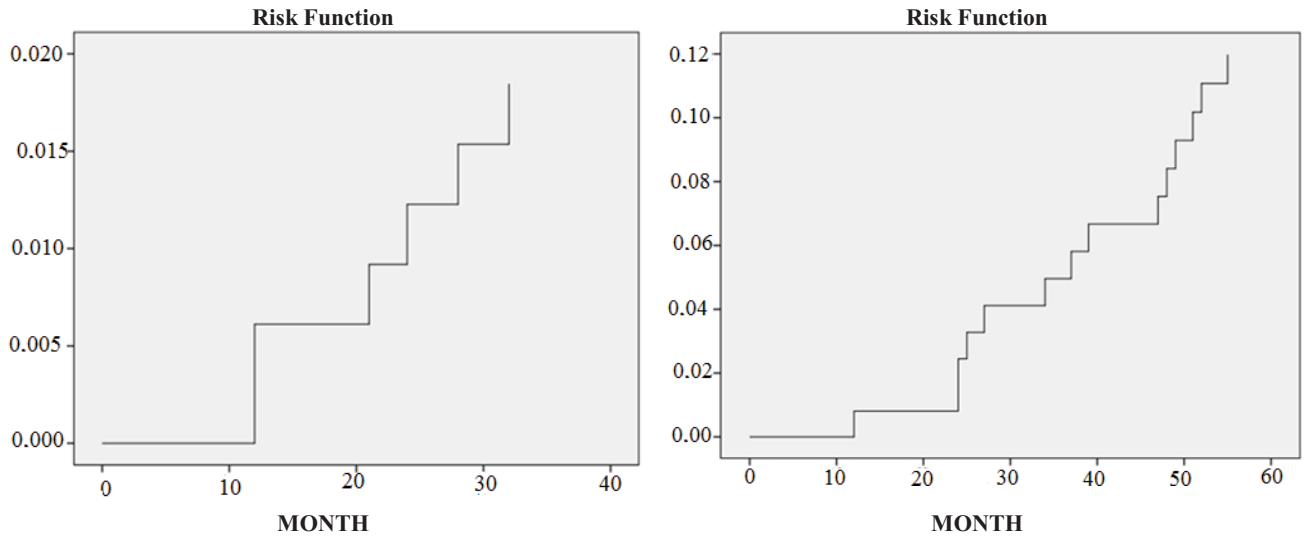

Figure 2. *Coronary events in patients with COPD during the observation period (moderate (left) and high (right) coronary risk)*

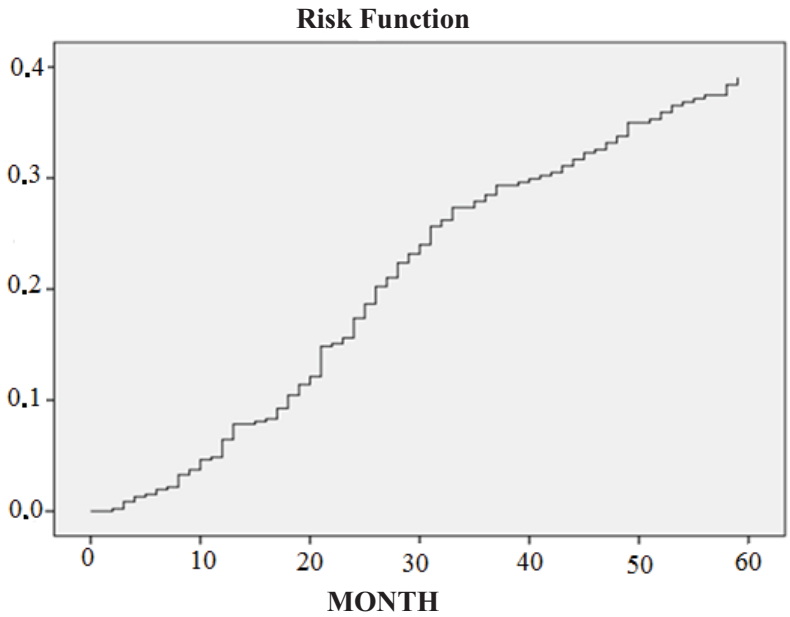

Figure 3. *Coronary events in patients with COPD during the observation period (very high coronary risk)*

In COPD patients making up the risk group for coronary events, no significant changes in respiratory function parameters were observed over five years (Table 3).

Most coronary events among COPD patients at moderate and high risk were reported during the first 3 years of observation, among patients at extremely high risk — evenly throughout 5 years. Coronary events were accompanied by the underlying disease exacerbations and more often were reported in the autumn-winter period. Their incidence (myocardial infarction, angina, coronary death) in COPD patients at extremely high, high and moderate coronary risk over five years was 33.9 %, 10.5 %, 1.52 %, respectively [22] (Figures 2, 3).

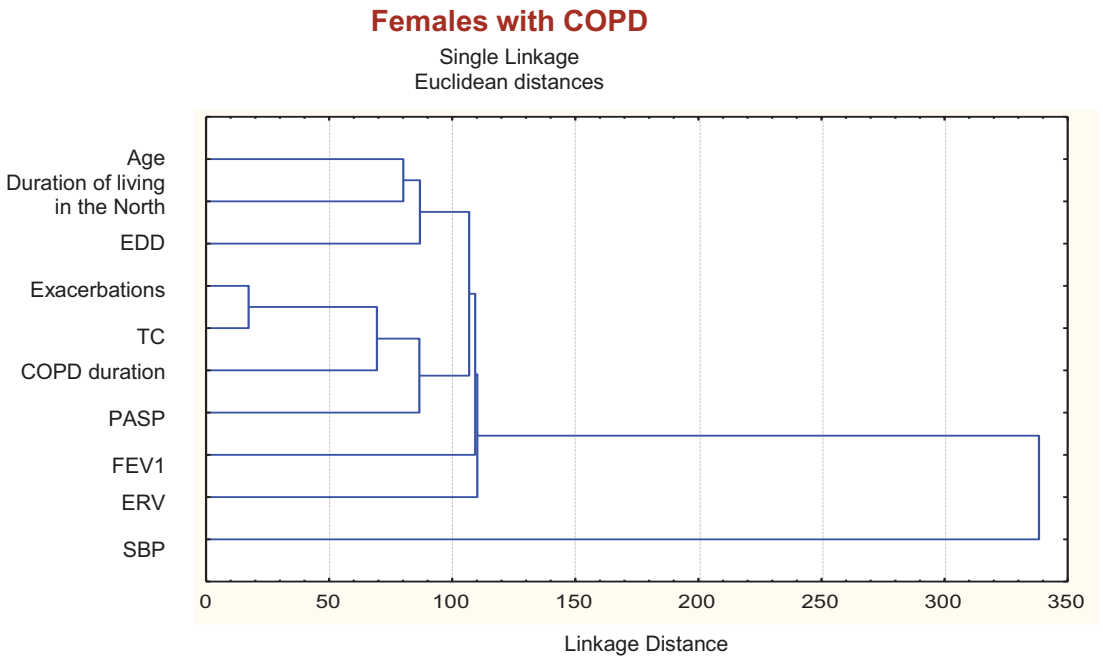

Figure 4. *Clusters of risk factors for coronary events in female patients with COPD*

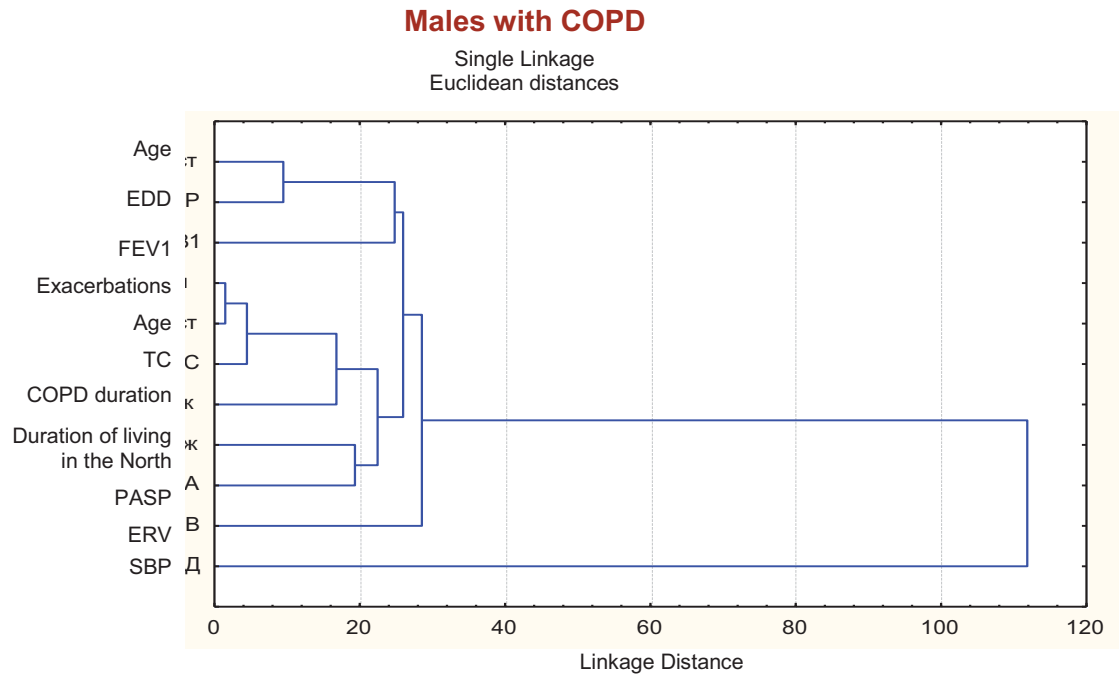

Figure 5. *Clusters of risk factors for coronary events in male patients with COPD*

The extended (body plethysmography, echocardiography) instrumental examination makes it possible to predict the risk of coronary events in COPD by identifying a high-risk group. Using stepwise discriminant analysis, it has been established that the key predictive markers of coronary events in the COPD patients living in northern latitudes are echocardiography data (left ventricular end-diastolic dimension (EDD_{LV}), pulmonary artery systolic pressure (PASP), most important for females (Figure 4)) and body plethysmography data (expiratory reserve volume (ERV), which is the most important for males (Figure 5)). The annual frequency of COPD exacerbations that required hospitalization was associated with the incidence of reported coronary events ($p<0.05$) both among males and females suffering from COPD.

Thus, the use of echocardiography and body plethysmography with the target assessment of volumetric parameters makes it possible to identify risk groups for coronary events and thereby prevent them in a timely manner.

Conclusion

There are a lot of studies that confirm the relationship between cardiovascular mortality and progressive worsening of obstructive respiratory function impairments, the main marker of which is FEV_1 [13–15, 19–21, 24–27]. However, in our view, when predicting coronary events in COPD patients, the progressive aggravation of volumetric respiratory function parameters, and consequently the progression of restrictive respiratory function impairments, is underestimated. The study of respiratory function in COPD patients has established that patients with lower volumetric respiratory function parameters, such as ERV (%), IC (%), had confirmed IHD over the five-year observation period ($p<0.05$). It is interesting that obstructive respiratory function impairments remained relatively stable over time. This suggests the need to perform body plethysmography in all COPD patients as an obligatory examination in order to identify latent restrictive respiratory function impairment at the very beginning of the disease. Endothelial dysfunction and vascular remodeling, which progressively worsen even during stable COPD, contribute to the development and progression of latent left ventricular failure, as evidenced by left ventricular myocardium remodeling [21–23], which undoubtedly leads to a coronary condition.

We have proved that COPD first manifests in patients after 20 and more years of living in the North. However, given the low diagnosis level of COPD in Russia and long asymptomatic progress of the disease, it may happen that using body plethysmography as screening of all smokers, COPD signs would be identified after a shorter period. Several authors have concluded that changes in lungs occur after 10 years of living under conditions of northern latitudes [1]. Thus, in the North, cardiorespiratory remodeling in patients with COPD includes permanent obstructive respiratory function impairment and reduction in lung volume, which, along with other risk factors, contributes to the development of coronary events.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Lutsenko M.T. Chronic lung disease in the north of Russia. Basic research. 2012; 4 (Part 1): 74-79. [in Russian].
2. Vatutin N.T., Smirnova A.S. Comorbidity of chronic obstructive pulmonary disease and cardiovascular disease: treatment features. Pulmonology 2016; 26 (3): 364-371 [in Russian].
3. Kutsenko M.A., Chuchalin A.G. Comorbidity Paradigm: syntropy of COPD and IBS. Russian medical journal. 2014; 5: 389-392. [in Russian].
4. Desalu O. O. Prevalence of self-reported allergic rhinitis and its relationship with asthma among adult. J. Investig Allergol. Clin. Immunol. 2009; 19(6): 474-480.
5. Popova M.A. Myocardial Infarction in the North: pathogen, clinic, diagnosis, treatment. Surgut. 2003; 180 p. [in Russian].
6. Kerry Schnell, Carlos O Weiss, Todd Lee. The Prevalence of Clinically relevant Comorbid Conditions in Patients with Physician-diagnosed COPD — A Cross-sectional Study Using Data from NHANES 1999-2008. BMC Pnlm Med. 2012; 12: 26.

7. Vertkin A.L., Skotnikov A.S., Gubzhokova O.M. Comorbidity in chronic obstructive pulmonary disease: the role of chronic systemic inflammation and the clinical and pharmacological niches of roflumilast. Attending doctor. 2013; 9: 20-24.
8. Correia, L. L., Lebedev A., Efremova O. A., Prewiev K. I., Litovchenko, E. S. the Problem of polymorbidity in combination chronic obstructive pulmonary disease and cardiovascular diseases. Scientific reports. 2013; 4(147), issue 21: 12-17. [in Russian].
9. Hole, D. J. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study / D. J. Hole, G. C. Watt, G. Davey-Smith [et al.]. Br. Med. J. 1996: 313; 711—715.
10. Karoli N.A., Rebrov A. P. Endothelial dysfunction and its clinical significance in patients with chronic obstructive pulmonary disease. Clinical medicine. 2005; 9: 10-16. [in Russian]
11. Santos S. Characterization of pulmonary vascular remodeling in smokers and patients with mild COPD. Eur. Respir. J. 2002; 19: 632-638.
12. The Relationship of vasomotor effects of the endothelium of the main and cerebral arteries in obstructive pulmonary diseases. Russian journal of physiology. I. M. Sechenov. 2008; 94(2): 206-211. [in Russian].
13. Persson C. Peak expiratory flow and risk of cardiovascular disease and death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. C. Persson, C. Bengtsson, L. Lapidus [et al.]. Am J Epidemiol. 1986: 124; 942–948.
14. Smith E.B. Fibrinogen, fibrin and arterial wall. E. B. Smith. Eur. Heart J. 1995; 11-15.
15. Anthonisen N.R., Connett J.E., Murray R.P. For the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. Am. J. Respir. Crit. Care Med. 2002: 166; 675–679.
16. Makarova M.A. Arterial stiffness and endothelial dysfunction in patients with chronic obstructive pulmonary disease. Pulmonology 2011; 4: 109-117. [in Russian].
17. Kulikov V.P. Clinical pathophysiology and functional diagnostics: a teaching method. Manual. Barnaul: Paragraph. 2004; 415 p. [in Russian].
18. Sin D.D. Surfactant protein D: a lung specific biomarker in COPD? Ther Adv Respir Dis. 2008: 2; 65–74.
19. Watson L. Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscope study. Respir. Med. 2006: 100, 4; 746-753.
20. Makris D. Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. Respir. Med. 2007; 101(6): 1305—1312.
21. Wiesel I. Yu. Results of dynamic observation of patients with chronic obstructive pulmonary disease (COPD) for 2-5 years. Literature review. Bulletin of modern clinical medicine. 2009; 2(1): 27-31. [in Russian].
22. Dolgopolova D.A., Popova M.A., Terentyeva N.N. Prediction of coronary events based on the analysis of the dynamics of the morphofunctional parameters of the cardiovascular system in patients with chronic obstructive pulmonary disease in the north. The Russian Archives of Internal Medicine. 2018; 8(1): 36-45. [in Russian].
23. Dolgopolova D.A., Popova M.A., Vedenkina I.V. Morphofunctional changes in the heart at different cardiovascular risks in patients with chronic obstructive pulmonary disease. In the world of scientific discoveries. 2012; 5.3(29): 55-69 [in Russian].
24. Dolgopolova D.A. Coronary risk in chronic obstructive pulmonary disease: new answers to old questions. Doctor-graduate student. 2015; 6.2 (73): 234-240. [in Russian].
25. Dolgopolova D.A., Popova M.A., Vedenkina I.V. Assessment of the possibility of using the SCORE scale in predicting cardiovascular events in patients with chronic obstructive pulmonary disease. Modern problems of science and education. 2014; 2: Electronic resource: URL: http://science-education.ru/ru/article/view?id=12951 (appeal date: 12/14/2018) [in Russian].
26. He J. Q. Associations of IL-6 polymorphisms with lung function decline and COPD. Thorax. 2009: 64; 698–704.
27. Pinto-Plata V.M. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax. 2006: 61; 23–28.

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