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Diagnostic and Prognostic Markers of Chronic Heart Failure in Patients With Occupational Chronic Obstructive Pulmonary Disease

Aim — Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are a common comorbidity. Professional chronic obstructive pulmonary disease (PCOPD) is a specific phenotype, which suggests peculiarities in the development of HF. Difficulties of HF diagnosis in such patients determine the relevance of searching for additional markers. The aim of the study was identifying HF markers in patients with PCOPD.

Material and methods — This single-site, cohort, prospective, observational study included 345 patients. The main group consisted of PCOPD patients; the comparison group consisted of patients with COPD induced by tobacco smoking; and the control group included conventionally healthy individuals. The groups were matched by the index of coincidence; pairs were matched at 1:1 by the «nearest neighbor index»; covariates for matching included COPD duration, sex, and age. Each group included 115 patients. The major professional adverse factors were silica-containing dust and organic solvents. COPD was diagnosed according to GOLD criteria; HF was diagnosed in accordance with Russian clinical guidelines. The markers were determined by multifactorial logistic regression. Likelihood of events with allowance for the time to the event was analyzed by the Kaplan-Meier method.

Results — HF in PCOPD patients was characterized by biventricular damage, preserved left ventricular ejection fraction, and frequent hospitalizations for decompensation (17.5% vs. 9.5% for COPD in smokers). HF markers in patients with PCOPD included the length of work of more than 20 years, pulmonary artery systolic pressure (PASP) higher than 35 mm Hg according to data of Doppler echocardiography, diffusing capacity of lungs for carbon monoxide (DLCO) less than 50%, increased serum concentrations of CC-chemokine ligand 18 (CCL18), S-100 beta protein, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Diagnostic sensitivity of the multifactorial model was 84% and specificity was 81%. Two models were proposed for purposes of screening, which included the following parameters: length of work, exposure to aromatic hydrocarbons, decreased distance in 6-min walk test by more than 60 m per year and length of work, exposure to inorganic dust, and decreased forced expiratory volume during the first second by more than 55 ml per year.

Conclusion — The markers for development of HF in PCOPD patients are length of work >20 years, PASP >35 mm Hg, DLCO <50%, and increased serum concentrations of CCL18, S-100 beta protein, and NT-pro-BNP.

Keywords — Heart failure; professional chronic obstructive pulmonary disease; diagnosis; prediction

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Concomitant chronic heart failure (HF) and chronic obstructive pulmonary disease (COPD) are among the most common comorbidities. According to various sources, the prevalence of COPD occurring in patients with HF varies from 8 to 41%, and that of HF occurring in patients with COPD varies from 16 to 70% [1–3]. In the comorbid condition of HF and COPD, the severity of both diseases increases, and the prognosis gets worse [4, 5].

Several mechanisms of the relationship between these two diseases have been established. Right ventricular (RV) failure can be a direct complication of COPD and develop due to the increased afterload accompanying the development of pulmonary hypertension (PH) [6]. COPD is a risk factor for cardiovascular diseases (CVD), which are etiological factors of CHF [2]. The anatomy of the thorax changes due to

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emphysema, causing the left ventricular (LV) diastolic dysfunction [7].

However, systemic inflammation is the most significant factor for development of HF in COPD. The immune response to inhaled pathogenic particles is accompanied, not only by remodeling of the respiratory system and development of COPD, but also by penetration of pro-inflammatory cytokines, free oxygen radicals, metalloproteinases, and profibrotic growth factors into the systemic circulation. Thus, the immune response contributes to the progression of hypertrophy and vascular fibrosis with increased LV afterload, myocardial fibrosis, and remodeling, all of which subsequently lead to cardiac dysfunction [8]. COPD is a heterogeneous condition in which the cellular-molecular mechanisms and systemic inflammatory activity can differ significantly in various cases. Occupational COPD (oCOPD) is the result of failure of adaptation when the lungs, acting as a barrier, interact with aggressive factors of the occupational environment, e.g., and industrial aerosols [9]. Several studies have shown the specificity of the inflammation and oCOPD phenotype [10], which suggests specific features of the development of comorbid HF.

There are screening programs focused on the detection of COPD. The diagnosis of HF in such patients is difficult because the symptoms are common in the two diseases [11]. Moreover, the levels of the standard diagnostic marker of HF, N-terminal pro-brain natriuretic peptide (NT-proBNP), can be increased in patients with COPD due to PH, which makes differential diagnosis more difficult [12]. Early definition of HF and timely effective therapy contribute to higher life expectancy and maintain patient working capacity. Thus, it is of immediate interest to study the pathogenic patterns and search for additional predictors of HF in patients with oCOPD. Therefore, the objective of this study was to identify markers of the development of HF in patients with oCOPD.

Material and Methods

A single-center, cohort, prospective observational study of 345 patients was performed. The main study group was comprised of patients with oCOPD (n=115). A comparison group was comprised of patients with smoking-related COPD (n=115) without occupational health risks. Levels of molecular markers in these two groups were compared with those of conditionally healthy individuals of a control group (n=115). The study was conducted under the ethical principles stated in the Helsinki Declaration of the World Medical Association and the ethical principles and regulations described in the 2002 Bulletin of the Higher Attestation Commission of the Russian Ministry of Education No. 3 «On the Procedure for Biomedical Research in Human Subjects.» The ethics committee of the Novosibirsk State Medical University approved the study. The study duration was 16 [12; 18] mos.

Patients were included in the study if they met the following criteria: 1) signed informed consent to participate in the study; 2) age from 45 to 70 yrs; 3) diagnosis of COPD (Global initiative for chronic Obstructive Lung Disease (GOLD)); 4) the ratio of the forced expiratory volume exhaled in 1 sec (FEV_1) to the forced vital capacity (FVC) after the inhalation of a broncholitic of 70% or less [13]. For the oCOPD group, inclusion required exposure of industrial aerosols above the maximum allowable concentrations (MAC) in the air of the working area and at least 5-yr employment history by the time of the first symptoms of COPD. For the comparison group, inclusion required at least a 5-yr history of smoking, a pack-year index of at least 10, and no occupational health risks. Exclusion criteria were: 1) bronchopulmonary disease other than COPD, but uncomplicated chronic bronchitis was allowable; 2) CVD and HF before the occupational exposure to industrial aerosols and the onset of respiratory symptoms; 3) infectious endocarditis, and other valvular heart diseases; 4) inflammatory myocardial diseases; 5) thyrotoxicosis; 6) diabetes mellitus; 7) grade III obesity; 8) contraindications to the diagnostic procedures. According to these criteria, 117 patients were included in the oCOPD group, and 121 patients were included in the comparison group. The study groups were formed using selection by index of compliance. A method of matching pairs 1: 1 using a «nearest neighbor» search. Duration of COPD, sex, and age were the comparison covariates. The resulting size of each of the three groups was 115 patients.

The association of COPD with the patient's occupation was evaluated at the Novosibirsk Center for Occupational Pathology (City Clinical Hospital No. 2). The hygienic analysis of the occupational environment was carried out according to R. 2.2.2006–05 «Guidelines for Hygienic Assessment of Occupational Environmental Factors and Labor Process. Criteria and Classification of Working Environment.» We used the data from sanitary and hygienic characteristics of the employee's working environment as developed by experts of the occupational hygiene and environmental sanitation department of the Novosibirsk office of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing. This was done at the time of the primary diagnosis of occupational disease

or from the results of the special assessment of working environment provided by employers. Patients with oCOPD were employees of mechanical engineering (OKVED 30.30) and glass production (OKVED 23.13) plants. The main adverse occupational factors were inorganic dust exceeding the maximum allowable concentrations by 2–9.7 times, organic solvents within the range of 1.5–6.5-fold MAC, and/or metal mist exceeding the MAC by 1.5 times. Warming microclimate, general and/or local vibration, and noise were other adverse occupational factors. The median duration of employment history was 26 [19; 36] yrs.

The assessment of smoking status showed that the percentage of smokers and former smokers were 30.4% (35 patients) in the oCOPD group and 32.2% (37 patients) in the control group, and 100% in the comparison group (p=0.002, versus the comparison group). The median duration of smoking history was 31 [26; 38] yrs in the oCOPD group, 32 [25; 40] yrs in the comparison group, and 30 [25; 37] yrs in the control group (p=0.76). The pack-year index was 25 [22; 33] in the oCOPD group, 29 [25; 37] in the comparison group, and 27 [23; 31] in the control group (p=0.08).

An indication of chronic HF was any echocardiographic signs of myocardial dysfunction and/or NT-pro-BNP <125 pg/ml [14]. RV, LV, or biventricular HF was defined based on the prevalence of symptoms and echocardiographic signs of the damage of a respective part of the heart. Decompensated HF was diagnosed in a rapid worsening of corresponding symptoms, which required emergency hospitalization and changes in therapy [14]. All patients were treated according to the Guidelines of the Russian Respiratory Society and GOLD 2018–2020. The characteristics of the subjects are detailed in Table 1.

Symptoms, findings of Doppler echocardiogram, serum concentrations of NT-pro-BNP were determined to identify the differences in HF in patients with oCOPD. The origin of HF was assessed by medical records. All patients were examined for symptoms, rate of exacerbations, results of lung function tests, induced sputum cytology, eosinophil count, pulmonary hemodynamics, hygienic parameters of the working environment, molecular markers of systemic inflammation, and organ damage to identify the factors associated with HF. The COPD assessment test (CAT) was used to evaluate the symptoms [15]. Exacerbations were defined according to the GOLD guidelines [13]. Lung function was tested using spirography with broncholitic test (according to ATS/ERS 2005 [16]), a 6-min walk distance (6MWD) test, a blood oxygen level (O2 saturation) test, a test of the diffusing capacity of the lung for carbon monoxide (DLCO) twice at the 12-mon interval, and body plethysmography.

Doppler echocardiogram was performed on a Mindray DC-N3 ultrasound scanner. RV and LV isovolumic relaxation time (IVRT), the ratio between early mitral inflow velocity and mitral early diastolic velocity (E/é), transmitral blood flow (E/A), left atrial volume index, maximal tricuspid regurgitation velocity, LV ejection fraction (LVEF), LV fractional shortening, LV end-diastolic and end-systolic dimensions, LV end diastolic and systolic volumes, RV basal dimension, RV systolic and diastolic area, RV fractional area change, atrial systolic dimensions, LV posterior wall and interventricular septum thickness, RV anterior wall thickness, RV outflow tract diameter, LV outflow tract diameter, tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery systolic pressure were determined. The systemic blood

Table 1. Characteristics of the study patients

Parameter	oCOPD (n=115)	Smoking-related COPD (n=115)	Control (n=115)	p
Age, yrs	61 [54; 63]	60 [55; 62]	57 [54; 59]	0.120
Sex, abs. (%)				
M	80 (69.6)	78 (67.8)	75 (65.2)	0.185
F	35 (30.4)	37 (32.2)	40 (34.8)	0.185
Race (caucasian), abs. (%)	115 (100)	115 (100)	115 (100)	1.000
Duration of COPD, yrs	11 [8; 14]	10 [8; 13]	–	0.433
FEV_1/FVC, %	61.2±3.10	54±4.53	102.5±6.13	0.011*
FEV_1, %	60.3±4.92	55.7±3.47	101.7±5.39	0.011*
Group by GOLD, abs. (%)				
A	2 (1.7)	5 (4.3)	–	0.048**
B	66 (57.4)	41 (35.7)	–	0.048
C	5 (4.3)	15 (13.0)	–	0.002
D	42 (36.5)	54 (47.0)	–	0.120

*, significantly different from the control group; **, the groups were compared using the Fisher's exact test; oCOPD, occupational chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume exhaled in 1 sec; FVC, forced vital capacity of the lungs.

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concentrations of chemokine ligand 18 (CCL18), total lactic dehydrogenase (LDG), troponin T, S-100 beta, NT-proBNP, von Willebrand factor, and C-reactive protein were determined by a sandwich enzyme-linked immunosorbent assay (8 channel Expert Plus microplate reader, 450 nm wavelength, test kits).

The findings were statistically processed using the SPSS 24.0 and Statistica 9.0 software suites. Normal distribution was verified with the Kolmogorov–Smirnov test. When more than two groups were compared, the Bonferroni correction was used. The descriptive statistic data are presented as the mean and the standard error (M±SE) for continuous variables with normal distribution, as the median and the interquartile range (Me [25th percentile; 75th percentile] for variables with non-normal distribution, and as a percentage for categorical variables. The groups with continuous variables were compared using the Kruskal–Wallis H-test.

Qualitative categorical variables were compare using the chi-square test. The analysis of event probability, taking into account the time-to-onset, was conducted using the Kaplan-Meier test. The intergroup differences were calculated using the Gehan test. Markers were identified by means of uni- and multivariate logistic regression analysis. Continuous variables were converted into dichotomic values, and the 25th or 75th percentile were cut-off points. Regression coefficient (B), odds ratio (OR), and 95% confidence interval (CI) were calculated. The significance of the coefficient's difference from zero was determined by Wald statistics. The predictive value was analyzed by constructing the ROC-curves showing the sensitivity and specificity ratio. If the area under the ROC curve was 50% or more, the specific ability of the model was acceptable. Differences were considered significant at $p < 0.05$.

Results

Due to smoking, the percentage of patients with HF was higher in the oCOPD group (63, 54.8%) than in the COPD group (41, 35.6%) (χ^2=6.2; p=0.002). All patients diagnosed with HF met the criterion of elevated serum NT-pro-BNP. The mean level was 2,195±122.5 pg/ml in patients with oCOPD and HF and 943±54.2 pg/ml in the comparison group (p=0.001). Changes in E/é and/or decreases in the left/RV ejection fraction were simultaneously observed in 61 (96.8%) patients of the oCOPD HF subgroup and 40 (97.6%) patients of in the COPD HF subgroup. In these subgroups: E/é was 16.2±5.03 and 13.5±3.12, respectively (p=0.01); RVEF was 70.3±4.92 and 55.1±4.30 (p=0.01), LVEF was 69.2±3.16 and 57.0±4.54, respectively (p=0.01).

Biventricular HF prevailed in patients with oCOPD, n=44 (69.8%). RV failure alone was observed in 15 (23.8%) patients. 4 (6.3%) patients had only LV failure. The number of cases of biventricular ventricular failure or isolated RV failure was comparable in the group of smokers with COPD: 19 (46.3%) and 17 (41.5%), respectively. 5 (12.2%) patients had isolated LV failure. The majority of HF cases had preserved LVEF 47 (74.6%) in patients with oCOPD and 23 (56.1%) in patients with COPD related to smoking (p=0.002).

Analysis of the origin of HF showed that its causes in patients with oCOPD were: coronary artery disease (CAD) combined with hypertension, 15 (23.8%) cases; PH, 15 (23.8%) cases; secondary cardiomyopathy (except those specified as the exclusion criteria), 14 (22.2%) cases; CAD, 12 (19.1%) cases; hypertension, 7 (11.1%) cases. The causes of HF in patients with COPD related to smoking were: related hypertension and PH, 14 (34.1%) cases; CAD combined with hypertension, 6 (14.6%) cases; CAD, 5 (12.2%) cases; secondary cardiomyopathy, 2 (5.0%) cases. In the course of the year, 11 cases of decompensated HF requiring hospitalization were reported in the oCOPD HF subgroup and 4 cases in the smoking-related COPD HF subgroup. Kaplan-Meier analysis determined that decompensated HF-free survival in patients with oCOPD was significantly higher than in smokers with COPD, 91 and 83%, respectively (p=0.032).

Univariate logistic regression analysis enabled us to determine the relationship between the risk of HF and hygienic parameters, the phenotype of oCOPD, and serum biochemical markers (Table 2). In patients with COPD related to smoking, the risk of HF was associated with severity of COPD symptoms: CAT <10 (OR 1.55, 95% CI 1.03–2.62; p=0.045); severity of bronchoobstruction, FEV_1 <50% (OR 1.69, 95% CI 1.15–3.51; p=0.040); 6MWD <350 m (OR 1.32, 95% CI 1.03–3.46; p=0.048); exacerbation of COPD within 12 mos (OR 1.39, 95% CI 1.74–2.08; p=0.048).

Multivariate logistic regression analysis showed that the risk of HF in patients with oCOPD was associated most with more than 20-yr employment history by the time of onset of respiratory symptoms, PH, DLCO <50%, elevated serum levels of CCL18, S-100 beta, NT-proBNP (Table 3). If the logistic regression equation was estimated as more than or equal to 0.55, the diagnostic sensitivity and specificity of the model were 84 and 81%, respectively. The area under the sensitivity-specificity curve was 0.89 (95% CI 0.83–0.95; p=0.001; Figure 1). The value of 2 log-likelihood

Table 2. Correlation of clinical functional and molecular markers with the development of HF in patients with oCOPD as shown by univariate analysis

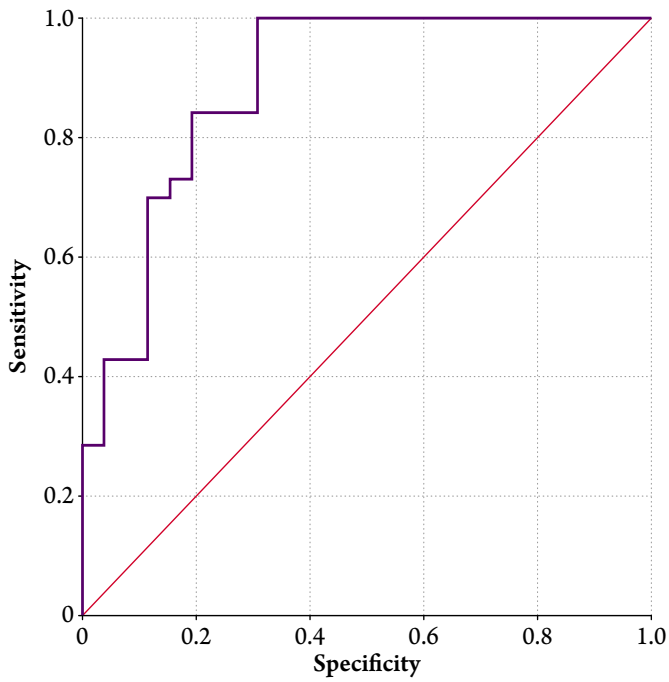
Parameter	OR	95% CI	Wald test	p
More than 20-yr employment history under occupational exposure to industrial aerosols by the time of onset of respiratory symptoms	3.31	1.21–9.01	5.43	0.020
Exposure to organic solvents	3.57	1.30–9.72	6.12	0.013
Exposure to inorganic dust	2.19	1.04–4.64	4.21	0.040
CAT <10	2.61	1.14–5.94	5.19	0.023
6MWD <250 m	2.32	1.07–5.00	4.55	0.033
Decrease in 6MWD more than 60 m a yr	2.42	1.02–5.70	4.04	0.044
FEV_1 <50%	2.78	1.06–7.26	4.34	0.037
Oxygen saturation at rest <95%	3.30	1.33–8.22	6.64	0.010
PASP <35 mmHg	3.57	1.31–9.72	6.18	0.013
DLCO <50%	2.83	1.03–7.83	4.03	0.045
Admissions for COPD within a yr	2.25	1.01–5.01	3.93	0.047
CCL18 <15 ng/ml	3.20	1.08–9.45	4.44	0.035
Troponin T <0.06 ng/ml	2.45	1.06–5.65	4.43	0.035
S-100 beta <0.25	5.3	1.11–10.06	4.40	0.036
NT-proBNP <125 pg/ml	3.8	1.16–12.12	4.88	0.027
von Willebrand factor <3.5 U/l	2.56	1.01–6.43	3.99	0.046

HF, heart failure; oCOPD, occupational chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; CAT, COPD assessment test, 6MWD, 6-mi walk distance; FEV_1, forced expiratory volume exhaled in 1 sec; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; PASP, pulmonary artery systolic pressure; CCL18, chemokine ligand 18; NT-proBNP, N-terminal pro-brain natriuretic peptide.

was 48.4, the Cox & Snell R-square was 0.445, and the Nagelkerke R-square was 0.495, i.e., the model explains up to 49.5% of the dispersion of HF prevalence.

Periodic screening requires low-cost, easy-to-use, and minimally time-consuming examination techniques. Two diagnostic models were developed using the eligible predictors. The first model included organic solvents contained in industrial aerosols (OR 1.5, 95% CI 1.02–7.78), more than 20-yr employment history (OR 1.4, 95% CI 1.04–7.05), and a decrease in 6MWD of more than 60 m/yr (OR 2.03, 95% CI 1.55–9.24). The combination of these three criteria allowed us to define HF in patients with oCOPD with 82% sensitivity and 71% specificity. The area under the sensitivity-specificity curve was 0.76 (95% CI 0.68–0.86, p=0.01). The second model included non-organic solvents contained in industrial aerosols (OR 2.5, 95% CI 1.74–4.30), more than 10-yr employment history in the specified environment (OR 1.5, 95% CI 1.1–3.49), and a decrease in FEV1 of more than 55 ml/yr (OR 2.6, 95% CI 1.3–5.29). HF was identified in patients with oCOPD by these three criteria with 80% sensitivity and 65% specificity. The area under the sensitivity-specificity curve was 0.72 (95% CI 0.62–0.81; p=0.005; Figure 2). The value of 2 Log likelihood was 68.2 and 70.1, respectively. The models explained 35.5 and 37.4% of HF dispersion, respectively.

Figure 1. ROC-curve of the multivariate model of the probability of heart failure in patients with occupational chronic obstructive pulmonary disease



Discussion

As mentioned earlier, the probability of HF in patients with oCOPD was correlated with the occupational environment, employment history, and

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АГ-артериальная гипертензия, ХСН-хроническая сердечная недостаточность

Сокращенная информация по применению лекарственного препарата Небилет®
Показания к применению: артериальная гипертензия; стабильная хроническая сердечная недостаточность легкой и средней степени тяжести (в составе комбинированной терапии) у пациентов старше 70 лет. **Способ применения и дозы:** внутрь, один раз в сутки, желательно в одно и то же время, независимо от времени приема пищи, запивая достаточным количеством жидкости. Средняя суточная доза для лечения артериальной гипертензии составляет 5 мг небиволола. Препарат Небилет® можно применять как в монотерапии, так и в комбинации с другими гипотензивными средствами. Лечение стабильной ХСН должно начинаться с постепенной титрации дозы небиволола до достижения индивидуальной оптимальной поддерживающей дозы. Начальная доза при этом – 1,25 мг/сут. Далее осуществляется титрование доз до 2,5 – 5 мг/сут, а затем до 10 мг/сут (максимальная суточная доза). **Противопоказания:** повышенная чувствительность к небивололу или к любому из компонентов препарата; печёночная недостаточность (класс В и С по классификации Чайлд-Пью) или нарушения функции печени; острая сердечная недостаточность; кардиогенный шок; хроническая сердечная недостаточность в стадии декомпенсации (требующая внутривенного введения препаратов, обладающих положительным инотропным действием); тяжелая артериальная гипотензия (систолическое АД менее 90 мм рт. ст.); синдром слабости синусового узла, включая синоаурикулярную блокаду; атриовентрикулярная (АВ) блокада **II** и **III** степени (без электрокардиостимулятора); брадикардия (ЧСС менее 60 уд/мин до начала терапии); нелеченная феохромоцитома (без одновременного применения альфа-адреноблокаторов); метаболический ацидоз; бронхоспазм и бронхиальная астма в анамнезе; тяжелые нарушения периферического кровообращения; непереносимость лактозы, дефицит лактазы и синдром глюкозо-галактозной мальабсорбции; возраст до 18 лет (эффективность и безопасность в этой возрастной группе не изучены); период грудного вскармливания; одновременное применение с флоктафенином, сультопридом (см. раздел «Взаимодействие с другими лекарственными средствами»). **С осторожностью:** почечная недостаточность тяжелой степени (скорость клубочковой фильтрации (СКФ) < 30 мл/мин/1,73 м2 площади поверхности тела); сахарный диабет; гиперфункция щитовидной железы; аллергические заболевания в анамнезе, псориаз; хроническая обструктивная болезнь легких; облитерирующие заболевания периферических сосудов (перемежающаяся хромота, синдром Рейно); атриовентрикулярная блокада **I** степени; стенокардия Принцметала; возраст старше 75 лет; артериальная гипотензия; феохромоцитома (при одновременном применении альфа-адреноблокаторов); хирургические вмешательства и общая анестезия; проведение десенсибилизирующей терапии; беременность. **Побочное действие** (ниже приведены часто встречающиеся нежелательные реакции). Нарушения со стороны нервной системы: головокружение, головная боль, парестезия. Нарушения со стороны дыхательной системы, органов грудной клетки и средостения: одышка. Нарушения со стороны желудочно-кишечного тракта: тошнота, диарея, запор. Общие расстройства и нарушения в месте введения: отеки, повышенная утомляемость. **Более подробную информацию см. в инструкции по медицинскому применению лекарственного препарата Небилет® от 05.02.2020.**

Список литературы:

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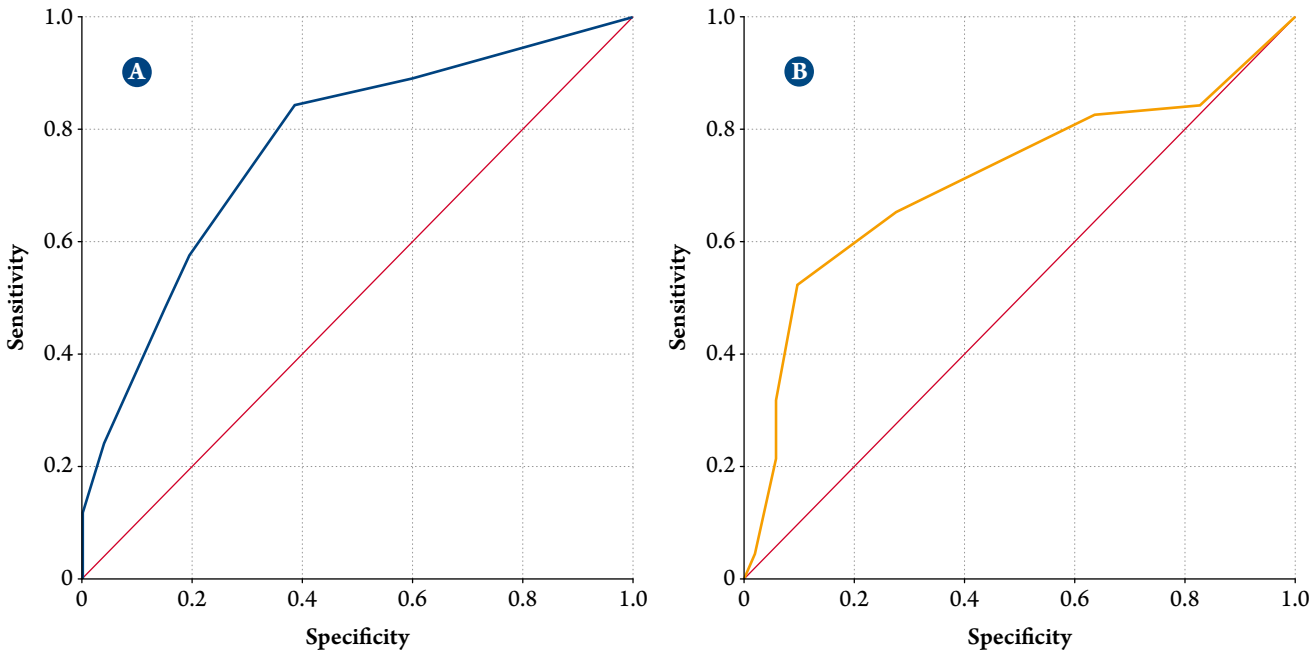
Table 3. Risk of HF in patients with oCOPD according to multivariate analysis

Parameter	B	OR	95% CI	Wald test	p
More than 20-yr employment history under occupational exposure to industrial aerosols by the time of onset of respiratory symptoms	1.50	4.45	1.19–4.32	4.95	0.026
PASP <35 mmHg	1.43	4.17	1.13–3.99	4.60	0.032
DLCO <50%	1.11	3.03	1.01–10.91	4.01	0.045
CCL18 <15 ng/ml	1.50	4.47	1.21–5.48	5.02	0.025
S-100 beta <0.25 μg/l	1.46	4.31	1.56–8.34	5.13	0.014
NT-proBNP <125 pg/ml	1.38	3.97	1.05–7.16	4.13	0.042

HF, heart failure; oCOPD, occupational chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; PASP, pulmonary artery systolic pressure; CCL18, chemokine ligand 18; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 2. ROC-curves of the models of screening diagnosis of heart failure in patients with occupational chronic obstructive pulmonary disease



A – exposure to organic solvents; B – exposure to silica-containing dust.

the clinical and functional pattern of respiratory pathology. The majority of subjects with COPD and comorbid HF with preserved LVEF, which was consistent with the data available in the literature [11]. It was also determined that the rate of this variant of HF was higher in oCOPD than in smoking-related COPD. Observations included biventricular failure without a clear predominance of RV or LV dysfunction, which might be due to systemic inflammation. The results of the molecular marker tests suggest that subclinical organ damage might be characteristic of systemic manifestations of oCOPD and comorbid HF. The subphenotype was associated with the markers of inflammation of the pulmonary parenchyma (CCL18) [17] and damage of the heart (troponin T) [18], brain (S-100 beta) [19], and endothelium (von Willebrand factor) [20]. The oCOPD phenotype and comorbid HF is characterized by a decrease in the diffusing capacity of the lung. Lung remodeling is more likely to be interstitial in comorbidities, which worsens systemic and tissue hypoxemia and contributes to systemic damage. The direct effect of cardiotoxic components of industrial aerosols, including organic solvents, on vessels and myocardium [21], and the proatherogenic effect of chemicals and dust [22, 23] may be the additional factors that determine the pattern of the development of HF in patients with oCOPD.

Previous studies showed that the combination of COPD and HF increased the severity of symptoms, reduced exercise tolerance, and increased the rate of COPD exacerbations and decompensated HF [24, 25]. The same patterns were observed in the study groups.

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However, the identified differences between the groups allowed us to develop a multiple logistic regression model to differentiate the oCOPD and HF comorbidities. Two screening diagnostic models were also developed based on the parameters that could be determined with minimal consumption of time. These models can be used in periodic screening of working patients with oCOPD to identify at-risk individuals who should be examined for HF. A single-center enrollment of patients is the main limitation of the study. The identified markers should be validated in independent patient cohorts.

Conclusion

Biventricular HF with preserved LV ejection fraction is a characteristic comorbidity with occupational COPD. An employment history of more than 20 yrs, pulmonary artery systolic pressure more than 35 mmHg, diffusing capacity of the lung for carbon monoxide less than 50%, serum CCL18 more than 15 ng/ml, serum S-100 beta more than 0.25 μg/l, NT-pro-BNP more than 125 pg/ml are markers of heart failure in patients with occupational COPD.

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