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IMPACT OF PULMONARY HYPERTENSION ON THE COURSE AND PROGNOSIS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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✓ ***Resume***

Chronic obstructive pulmonary disease (COPD) is one of the main causes of chronic morbidity and mortality worldwide [1,2]. The presence of pulmonary hypertension (PH) in COPD is associated with an increase in mortality, the risk of repeated hospitalizations, and an increase in healthcare costs for the treatment of this category of patients [3, 4]. PH in COPD is more often mild to moderate [5,6], but some patients have severe PH that is "disproportionate" to the degree of airflow limitation [6].

Keywords: chronic obstructive pulmonary disease, pulmonary hypertension, obstruction, predictors.

ВЛИЯНИЕ ЛЕГОЧНОЙ ГИПЕРТЕНЗИИ НА ТЕЧЕНИЕ И ПРОГНОЗ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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✓ ***Резюме***

Хроническая обструктивная болезнь легких (ХОБЛ) является одной из основных причин хронической заболеваемости и смертности во всем мире [1,2]. Наличие легочной гипертензии (ЛГ) при ХОБЛ ассоциируется с повышением летальности, риска повторных госпитализаций, увеличением затрат здравоохранения на лечение данной категории пациентов [3, 4]. ЛГ при ХОБЛ чаще бывает легкой и умеренной [5,6], однако у некоторых больных встречается тяжелая ЛГ, "непропорциональная" степени ограничения воздушного потока [6].

Ключевые слова: хроническая обструктивная болезнь легких, легочная гипертензия, обструкция, предикторы.

ЎПКА ГИПЕРТЕНЗИЯСИНИ СУРУНКАЛИ ЎПКА ОБСТРУКЦИЯСИ КАСАЛЛИГИ БИЛАН ОҒРИГАН БЕМОРЛАРДА КАСАЛЛИКНИНГ КЕЧИШИ

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✓ ***Резюме***

Сурункали ўпка обструкцияси касаллиги (СЎОК) сурункали касаллик ва бутун дунёдаги ўлима олиб келувчи касалликлардан бири бўлиб ҳисобланади [1,2]. Ушбу касалликлар бирга келган ҳолатда леталлик даражаси, қайта госпитализация хавфи ошиб, ушбу ҳолат шу касалликни даволашга нисбатан кетадиган сарф-харажатларни ошишига олиб келади [3, 4]. СЎОК ва ХОБЛ бирга келганда, у кўп ҳолларда енгил ёки ўртача даражада бўлади [5,6], аммо айрим беморларда СЎОК нинг огир "номутаносиб" тури учраб, у ҳаво оқимининг чекланишига олиб келади [6].

Калит сўзлар: сурункали ўпка обструкцияси касаллиги, ўпка гипертензияси, обструкция, предикторлар.

Relevance

Chronic obstructive pulmonary disease (COPD) is one of the main causes of chronic morbidity and mortality worldwide [1,2]. The presence of pulmonary hypertension (PH) in COPD is associated with an increase in mortality, the risk of repeated hospitalizations, and an increase in healthcare costs for the treatment of this category of patients [3, 4]. PH in COPD is more often mild to moderate [5,6], but some patients have severe PH that is "disproportionate" to the degree of airflow limitation [6].

The aim of this study was to study the features of the clinical course, predictors of repeated hospitalizations and mortality in patients with COPD, depending on the presence and degree of PH.

Material and methods

The study included 88 patients with COPD (II-IV severity according to the GOLD spirometric classification [1]; men — 76, women — 12; mean age 59.5±9.27 years; smoking experience 23.1±11.42 packs /year; frequency of exacerbations during the year 2.4±0.89; BMI 27.2±12.06 kg/m2). The criterion for PH, taking into account the parameters of Doppler echocardiography, was an increase in systolic pressure in the pulmonary artery (SPPA) >40 mm Hg. at rest. Patients were divided into three groups depending on the presence and degree of increase in SPPA: group 1 without PH (SPPA <40 mm Hg, n=168), group 2 with moderate PH (SPPA 40-55 mm Hg). .st., n=101), group 3 — with severe PH (SPPA >55 mm Hg, n=19). Exclusion criteria from the study were: chronic heart failure (with ejection fraction (EF) of the left ventricle <50%), portal hypertension, pulmonary embolism, connective tissue disease, HIV infection.

Patients were included in the study only after signing informed consent. COPD was diagnosed according to the GOLD guidelines [1]. All patients were assessed demographic indicators, smoking intensity, body mass index, symptoms, data of an objective, laboratory and instrumental examination, concomitant diseases, the number of exacerbations during the last year were determined. To assess the nutritional status of patients, the body mass index (BMI) was used, which was calculated according to the generally accepted formula: BMI=body weight (kg)/height (m2). A modified British Medical Research Council (mMRC) questionnaire and a COPD Assessment Test (CAT) were used to assess symptom severity, exercise tolerance was assessed using a 6-minute walking test (6MST) followed by determining the severity of dyspnea on the Borg scale [1]. Pulse oximetry (SpO2) was performed using an Onyx 9500 pulse oximeter (Nonin Nonin Medical, Inc., USA) before and after the 6-minute walking test.

Comprehensive assessment of respiratory function (RF) included computed spirometry with determination of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio; body plethysmography with determination of total lung capacity (TLC), residual lung volume (RRL), intrathoracic volume (VGO), TRL/RTL ratio); studies of the diffusion capacity of the lungs (DSL) by the method of a single breath, determination of the ratio LDL / alveolar ventilation (AV). The measurements were carried out on the equipment "Master Screen Body" (Erich Jaeger, Germany).

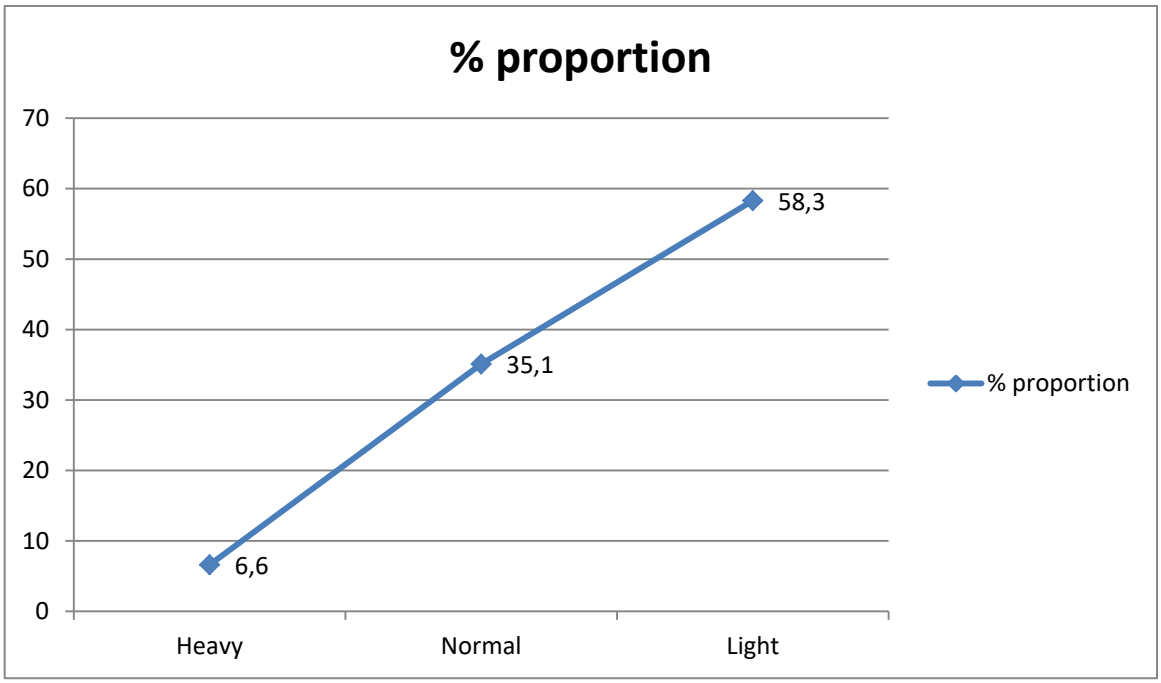
An echocardiographic study (EchoCG) of the heart was performed using a Philips En Visor CHD device (Holland) using standard accesses, standard hemodynamic parameters were studied. Assessment of diastolic ventricular function was performed using pulsed wave Doppler. The control volume was established in the cavity of the left ventricle at the level of the ends of the mitral (MV) and tricuspid (TC) valves. The rates of early (E) and late (A) diastolic ventricular filling and the E/A ratio were measured. Determination of the maximum systolic pressure in the pulmonary artery (PSAP) was carried out using continuous wave Doppler. The systolic pressure gradient between the right ventricle (RV) and the right atrium (RA) was calculated using the Bernoulli equation using the peak flow rate of tricuspid regurgitation. The sum of the transtricuspid gradient and RA pressure was taken equal to SPPA (in the absence of pulmonary valve stenosis). According to the ESC/ERS (2016) recommendations, the criterion for PH was SPPA ≥40 mmHg. [7].

Statistical data processing was performed using the Statistica V.7.0 software package (Statsoft Inc, USA). For all available samples, an analysis was made of the correspondence between the type of distribution of quantitative characteristics and the law of normal distribution using the Shapiro-Wilk test. If the distribution of features in the groups corresponded to the normal distribution law, the parametric Student's t-test was used to compare the group means. Otherwise, the comparative analysis of the groups was carried out using non-parametric methods. Differences were considered statistically significant at $p<0.05$. The dependence of quantitative indicators was assessed using correlation analysis.

Result and discussion

An increase in SPPA was noted in 120 patients (41.7%); moderate PH was recorded in 101 (35.1%) patients, severe PH in 19 (6.6%) patients (Fig. 1).

Rice. 1. The prevalence of PH in patients with COPD.



The groups of patients did not differ in age, duration of the disease. However, the intensity of smoking and the frequency of exacerbations of the disease during the year were statistically significantly higher in patients with severe PH compared with patients without PH and moderate PH. Severe PH was observed mainly in patients with GOLD functional grade IV, while moderate PH was observed in half of the cases in patients with both grade III and IV COPD. Depending on the degree of COPD, the level of SPPA in the studied patients was distributed as follows: in patients with grade II, the average SPPA was 33.5±10.37 mm Hg, with grade III — 35.8±10.23 mm Hg. ., with IV degree — 45.7±9.48 mm Hg. Complaints of coughing were noted in almost all patients of the study groups, hemoptysis was observed only in the group of patients with severe PH. Shortness of breath of varying severity was observed in all patients. The patients also complained of pain and discomfort, tightness in the heart area (Table 1), decreased exercise tolerance, and edema of the lower extremities. Phenomena of changes in the phalanges of the fingers according to the type of "drumsticks" and the chest according to the type of emphysematous occurred in 26 (15.4%) and 52 patients (30.9%) without PH, in 48 (47.5%) and 69 patients (68.3%) with moderate PH, in 19 patients (100%) with severe PH. Swelling of the jugular veins, hepatomegaly, peripheral edema, emphasis of the II tone on the pulmonary artery were mainly observed in patients of the 2nd and 3rd groups. Ascites developed in 2 patients (10.5%) with severe PH.

In patients with COPD, there was a significant increase in the severity of symptoms as PH appeared and worsened. The severity of symptoms according to the results of mMRC and the CAT assessment test in patients without PH was 3.1±0.41 points and 27.1±6.30 points, in patients with moderate PH - 3.32±0.49 points and 29.5 ±5.62 points, in patients with severe PH — 3.9±0.32 points and 33.3±4.78 points, respectively. Functional exercise tests also revealed a decrease in exercise tolerance as PH appeared and increased in severity. The average spirometric parameters in the groups of patients without PH and moderate PH corresponded to III (severe) severity. FVC was 66.5±17.95% and 61.6±16.13% predicted; FEV1 — 38.7±16.89% and 32.9±15.71% predicted; FEV1/FVC — 44.3±12.17% and 42.6±11.47%, respectively. The most significant VDF disturbances were observed in patients with severe PH. Thus, the FVC indicator was significantly lower, on average it was 49.7±15.88% of the due values (p2-3=0.001, p1-3=0.001); FEV1 corresponded to the IV degree of severity, averaged 27.2±13.72% of the due values (p2-3=0.05, p1-3=0.001); FEV1/FVC ratio — 46.2±13.10 (p2-3=0.23, p1-3=0.87).

Determination of lung volumes showed a statistically significant increase in the TEL in patients with severe PH compared with that in patients of the 1st and 2nd groups; an increase in TRL in patients with moderate and severe PH, compared with TRL in the group of patients without PH. Correlation analysis revealed only moderate negative correlations between the level of SPAP and FVC (r=-0.31, p=0.05), FEV1 (r=-0.36, p=0.04), MRL (r=-0.32 , p=0.05), DSL (r=-0.34, p=0.03), AV (r=-0.36, p=0.04); positive correlations — with REL (r=0.29, p=0.05).

The study of hemodynamics revealed an aggravation of the processes of remodeling of the right and left parts of the heart, systolic, diastolic dysfunction of both ventricles, thickening, paradoxical movements of the interventricular septum, the severity of tricuspid regurgitation as the severity of PH appeared and increased. Using Cox proportional hazards regression analysis, predictors of the next hospitalization of patients with COPD over the next 3 years and mortality were identified. The predictors of readmissions were the level of SPPA (RR 1.24; 95% CI 1.0-1.1; p = 0.02) and the concentration of CRP (RR 1.17; 95% CI 1.0-1.15; p =0.04). With regard to mortality in COPD patients, the severity of COPD symptoms on the CAT scale (RR 1.36; 95% CI 1.2-1.5; p=0.001), dyspnea on the Borg scale (RR 3.69; 95 % CI 1.1–0.9; p=0.001), exacerbation rate per year (RR 4.37; 95% CI 2.1–8.9; p=0.001), SPAP (RR 1.34; 95% CI 1.0-1.1; p=0.009), CRP concentration (RR 1.18; 95% CI 1.1-1.2; p=0.001), fibrinogen (RR 1.25; 95% CI 1, 0-1.5; p=0.009), NT-proCNP (RR 1.32; 95% CI 1.2-2.6; p=0.001) and NT-proBNP (RR 1.6; 95% CI 1, 7-6.9; p=0.001). Comparative analysis of the frequency of repeated hospitalizations of COPD depending on the presence of PH with a follow-up period of 3 years showed that the interval between hospitalizations in patients with PH is statistically significantly shorter than in the group of COPD patients without PH (log-Rank=-4.55, p=0.001).

Hospital lethality of the studied patients with COPD was 19 (6.59%) people. Analysis of the Kaplan-Meier survival curve in COPD patients with PH showed that the survival function in patients with moderate PH was statistically significantly higher than in the group of patients with severe PH (log-Rank=-4.96, p2-3=0.001). moderate PH was recorded, severe PH occurred in 6.6% of patients, which does not contradict the results of other studies [6,7]. The intensity of smoking and the frequency of exacerbations of the disease during the year were significantly higher in patients with severe PH compared with patients without and moderate PH. The presence of PH in COPD impairs gas exchange, increases dyspnea, and leads to the development of pancreatic dysfunction and peripheral edema [8]. One study showed that the reduction in the area of the capillary bed in COPD patients with severe PH significantly limits their physical activity [9].

In our study, clinical symptoms and signs indicating the presence of PH, the severity of dyspnea according to the results of mMRC, the CAT assessment test, the Borg scale, decreased exercise tolerance, blood desaturation after exercise increased as the severity of PH appeared and increased. Other studies have shown a high incidence of PH in patients with emphysema [10]. It is believed that the development of PH in COPD is caused by a reduction in the area of the capillary bed, which accompanies the destruction of the lung parenchyma and is characteristic of emphysema, and compression of the pulmonary vessels as a result of severe pulmonary hyperinflation (the effect of creating Vesta II zones), which is also observed in severe emphysema [9]. For COPD patients with severe PH, the characteristic functional features were: a significant decrease in the diffusion capacity of the lungs, severe hypoxemia without hypercapnia, and a moderate decrease in FEV1 (about 50%) [11].

In the COPD patients with PH studied by us, a significant change in the structure of the TFR was observed due to a pronounced increase in the TRL, a decrease in the FVC, FEV1, diffusive capacity of the lungs and the volume of alveolar ventilation. Functional disorders of pulmonary ventilation were more pronounced in the group of COPD patients with severe PH, which is confirmed by moderate correlations between the parameters of the comprehensive study of respiratory function and SPPA. Our data do not contradict the results of previous studies [11].

Remodeling of the pulmonary arteries in patients with COPD, which accompanies the development of PH, occurs already at the early stages of the disease [12]. So, despite the fact that severe PH in the present study was recorded mainly in patients with grade IV GOLD, in 10.5% of cases it was observed in patients with grade II and in 15.8% of patients with grade III GOLD. Moderate PH was observed in half of the cases in patients with both III and IV degrees of GOLD, in patients with II degree moderate PH was observed in 4.9% of cases.

In the patients we studied, the study of central and intracardiac hemodynamics showed that structural and functional changes in the right and left parts of the heart worsen as the disease

progresses and PH increases. However, the revealed changes in the geometric and functional parameters of the heart in the group of COPD patients without PH indicate that PH is not the only cause of heart remodeling in COPD patients [13].

PH in COPD patients worsens exercise tolerance and is a predictor of hospitalization and mortality [8, 14]. A number of authors have shown that age, presence of cor pulmonale, severe degree of bronchial obstruction, frequent hospitalizations, and concomitant diseases are the determinants of the risk of death in severe COPD [15]. The present study showed that pulmonary artery systolic pressure and CRP levels are predictors of readmissions; Predictors of mortality were the severity of symptoms on the CAT scale, dyspnea on the Borg scale, the frequency of exacerbations during the year, SPPA, the concentration of CRP, fibrinogen, NT-proCNP and NT-proBNP. An increase in the frequency of repeated hospitalizations in patients with COPD with PH and a significant deterioration in the survival of patients with severe PH were revealed.

Conclusion

Thus, PH in COPD patients in most cases is moderate, increases the severity of clinical manifestations, hemodynamic disorders, has only moderate correlations with impaired respiratory function, increases the frequency of hospitalizations and the risk of mortality. Survival of COPD patients with PH depends on its severity.

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