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# Concomitant chronic obstructive pulmonary disease and hypertension: reciprocal aggravation and high risk of cardiovascular complications

**Key words:** *chronic obstructive pulmonary disease, arterial hypertension, cardiovascular risk.*

Chronic obstructive pulmonary disease (COPD) is a common disease of mankind which has significant negative impact on quality of life and high incidence of hospitalizations and mortality. According to GOLD recommendations (2011) and Order of the Ministry of Health of Ukraine No. 555 dated June 27, 2013 we have new understanding of COPD as a disease that may be prevented and treated and the severity of which in some patients is preconditioned with its recurrence and concomitant conditions. In fact, these documents have summarized numerous studies that have shown the prevalence of comorbidities in COPD patients and their impact on the prognosis [3, 6]. The most common comorbidities in COPD are cardiovascular pathologies, such as coronary artery disease (CAD), arterial hypertension (AH), atrial fibrillation and heart failure (HF) [2, 9].

Concomitant COPD and related cardiovascular diseases result in higher incidence of admissions to hospital within a year due to any diseases [4, 5, 7]. According to Csaba Farsangetall (2012), the prevalence of HF is 4 times, CAD – 2 times, stable angina and myocardial infarction – 2,5 times, peripheral vascular disease – 2,4 times, stroke – 1,5 times higher in patients with COPD compared with the general population [4, 5].

The Cardiovascular Health Study (2006) revealed that patients with reduced function of external respiration were diagnosed AH in 33,8 % of cases, there was a direct relationship between AH, body mass index (BMI) and levels of C-reactive protein, thus indicating that role of systemic inflammation in development of COPD and concomitant AH [5, 6]. Therefore, the patients with COPD demonstrated

pathogenetically-reasonable mechanisms of higher cardiac risk, which were caused by both significant prevalence of comorbid cardiovascular disease and functional indexes of external respiration and increased markers of systemic inflammation, which were a predictor of early atherogenesis.

It was proven that comorbidity with COPD played significant role in higher incidence of mortality, especially due to cardiovascular diseases and cancer. The higher was the degree of comorbidity, the lower quality of life parameters we observed [8]. Given all above mentioned, COPD is considered an additional independent risk factor for cardiovascular complications.

## Objective of the study

The objective of the study was to establish the prevalence of risk factors for cardiovascular events in patients with COPD alone and in combination with AH, and to assess the impact of COPD on the course of AH.

## Material and methods

We examined 256 patients with concomitant COPD and AH, mean age ( $60,5 \pm 0,6$ ), including 158 (61,7 %) male patients of mean age ( $59,6 \pm 2,6$ ), and 98 (38,3 %) female patients of mean age ( $61,9 \pm 1,2$ ) (I group). II group consisted of 50 patients with AH without history of concomitant obstructive pulmonary disease, mean age – ( $60,6 \pm 1,5$ ), including 20 (40,0%) male subjects and 30 (60,0%) female subjects, average duration of AH – ( $11,96 \pm 1,82$ ), II Grade AH – 34 (68 %), and III Grade AH – 16 (32 %). The patients were subjected to standard clinical examination, over-the-

clock ECG and blood pressure (BP) monitoring was done using DiaCard 03500 unit (AOZT Solvieg, Kyiv) according to standard procedure. Indicators of intracardiac hemodynamics and duplex scanning of extracranial vessels were determined by echocardiography and pulse-wave Doppler method using 3,0–3,6–6,6 MHz sensors of Logiq-500 unit (GE, USA) according to standard procedure. We used standard protocol of echocardiography for assessment of dimensions of cardiac chambers in parasternal and apical positions over long and short axes and for measuring the intima-media complex thickness (IMCT). To assess the endothelial mechanism of vascular tonus regulation we used a sample of current-dependent (endothelium-dependent) vasodilation according to D.Celemajer et al., 1992. Quantitative assessment of C-reactive protein in serum was done using a Biomerica (USA) set by hsCRP ELISA method. Quantitative assessment of nitric oxide metabolites based on enzymatic conversion of nitrate to nitrite via nitrate reductase under Gris reaction was done using commercial test system – the RDS set for assessment of NO/NO<sub>2</sub>/NO<sub>3</sub> combination (UK).

Statistical analysis of the results was made on a personal computer using the statistical software package SPSS 12.0 for Windows, Grand Pack, Serial Number 9593869) (Buyul A. Tsefel P., 2005., Nasledov A.D., 2007). The investigated values are presented as «mean ± standard error of the average» ( $M \pm m$ ) or «mean ± standard deviation» ( $M \pm$ ). The reliable figures were considered the results of comparison with the probability of error (P) less than 0,05.

## Results and discussions

We have analyzed the incidence of various risk factors for cardiovascular complications and comorbidities in different study groups. It was noteworthy that the body mass index

(BMI) did not differ significantly in all groups, but patients with COPD had more subjects with BMI up to 18,5 kg/cm, the vast majority of patients had a BMI over the normal range with most patients with BMI over 40 kg/cm in the I group. Therefore, among the patients with AH and concomitant COPD examined by us dominated those with excessive body weight and different degrees of obesity.

No significant differences were observed in terms of a number of smoker patients, for example 100 (39,1 %) patients from I group were smokers, smoking index was ( $25,17 \pm 2,84$ ). In the second group there were 20 (40 %) such patients, smoking index – ( $28 \pm 6,39$ ). We noted the difference in gender prevalence of smoking. Group I had significantly more male smokers – 92 (35,9 %) ( $p = 0,037$ ), whilst the second group had 13 (26 %) male smokers. At the same time female smokers dominated in the second group, i.e. 7 (14 %) subjects, and 8 (3,13) ( $p = 0,023$ ) such subjects in group I. This suggests that smoking today plays key role in the development of pathological process both under the obstructive respiratory diseases and AH.

The most common comorbidities that affect the prognosis and stratification of cardiovascular risk are CAD and diabetes mellitus. The diabetes mellitus was significantly more often diagnosed in patients with comorbid disorders, both in group I in 61 patients (23,8 %) and in group II in 5 (10 %) patients,  $p < 0,001$ . 136 (53,1 %) patients from group I and 12 (24%) from group II,  $p < 0,001$  were diagnosed various types of CHD (Figure 1).

Among examined patients we found the history of myocardial infarction in 54 (21,1 %) patients from group I and in 5 (10 %) patients from in group II,  $p = 0,05$ . Clinically significant atherosclerosis of lower limb arteries was diagnosed in 27 (10.5 %) patients from group I and in 5 (10 %) patients from

**Table 1**  
Characteristics of the main risk factors in patients with hypertension and concomitant chronic obstructive pulmonary disease

Показник	I group, COPD and AH patients (n = 256)		II group, AH patients (n = 50)	
	abs	%	abs	%
BMI, kg/cm <sup>2</sup>	31,5 (27,4; 35,1)		30,8 (29,0; 33,9)	
BMI до 18–5	2	0,78	0	0
BMI 18,5–24,9	25	9,77	1	2
BMI 25–29,9	79	30,8	15	30
BMI 30–34,9	82	32,0	24	48
BMI 35–39,9	41	16,0	8	16
BMI > 40	27	10,5	2	4
Number of patients-smokers	100	39,1	20	40
Number of men-smokers	92	35,9	13	26
Number of females-smokers, abs	8	3,13	7	14
Smoking Index, pack/year	25,17 ± 2,84		28 ± 6,39	

Note: the quantitative indicators are presented as ( $M \pm m$ ) – mean ± standard error of the average and as Med (per 25; per 75) – median and inter-quartile space (25 and 75 percentile).

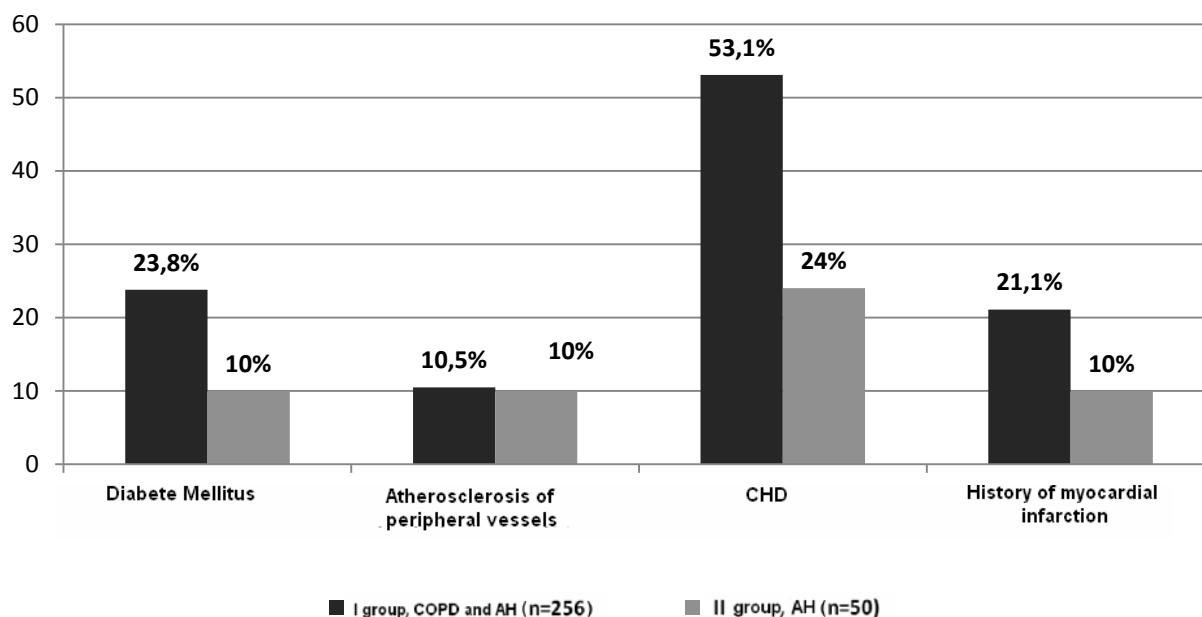


Figure 1. The prevalence of comorbidities in patients with COPD and concomitant AH and comparison groups

group II,  $p = 0,03$ . Therefore, patients with comorbid disorders were diagnosed concomitant CHD, diabetes mellitus, and atherosclerosis of lower extremities significantly more often, thus indicating high cardiovascular risk in this group of patients.

Among other factors of cardiovascular risk, dyslipidemia was diagnosed in 151 (59 %) patients of group I and in 12 (24 %) patients of group II,  $p = 0,005$ . All examined patients had significantly higher levels of C-reactive protein in contrast to the control group (practically healthy persons without history of COPD and AH). Among patients with COPD and concomitant AH we observed a 7,88 times growth of C-reactive protein, that was significantly higher than in patients with AH ( $p = 0,0005$ ). We mentioned positive correlation between the level of C-reactive protein and the severity of COPD ( $r = 0,28$ ;  $p < 0,0001$ ). Systemic inflammation played significant role in the development of the pathological process both in AH and in COPD, and patients with comorbid disorders had reciprocally-aggravated mechanisms that significantly contributed to further development of systemic inflammation signs.

Assessment of humoral component of endothelial dysfunction revealed reduction of nitrite/nitrate ( $\text{NO}_2 + \text{NO}_3$ ) metabolites and increase of endothelin -1 in patients with COPD and concomitant AH; we observed a correlation between lower levels of nitrite/nitrate metabolites and severity of COPD ( $r = 0,41$ ;  $p < 0,002$ ) and between higher volume of endothelin-1 and severity of AH ( $r = 0,39$ ;  $p < 0,0003$ ). While assessing endothelium-dependent vasodilation we found that patients with concomitant COPD and AH demonstrated increase in the velocity of systolic flow ( $p = 0,0008$ ) and diastolic flow (Vd) ( $p = 0,034$ ). The lowest increase in brachial artery after compression was diagnosed in group I – 3,5 % and 4,2 %,  $p = 0,03$  – in group II.

We found that 65 (25,4%) patients from group I and 19 (38 %) from the second group had normal vasoconstrictive reaction of brachial artery. At the same time decreased reaction

and vasoconstriction was diagnosed in 191 (74,6 %) from group I and in 31 (62 %) patients from group II,  $p = 0,003$  (Fig. 2.).

Therefore, we found that 190 (74,6 %) patients with comorbid disorders had signs of endothelial dysfunction. There are certain peculiarities of endothelial dysfunction preconditioned by disorder of various mechanisms of regulation of vascular tonus, including metabolic and endothelial ones. The proof of this is the meager increase in the diameter of the brachial artery and significant proportion of patients with reduced reaction to the test for hyperemia of brachial artery and increased proportion of patients with comorbid disorders and arterial vasoconstriction.

According to the results of Doppler echocardiography, the most significant changes were detected while assessing remodeling both left and right ventricles. 142 patients (55,5 %) with COPD and concomitant AH were diagnosed concentric hypertrophy of left ventricle. This trend was observed in patients with isolated AH, namely in 32 patients (64,0 %); the patients with combined course of diseases had increased number of subjects with eccentric left ventricular hypertrophy – 39 (15,2 %), thus indicating the volume overload of left ventricle correlated with the dimensions of the left atrium ( $r = 0,46$ ;  $p = 0,001$ ) (Table 2).

Structural and geometric remodeling of the right ventricle (volume overload type) under combination of COPD and AH was diagnosed in 117 patients (45,7 %) that was significantly higher than in patients with AH – 15 subjects (30,0 %) ( $p = 0,040$ ). Significantly higher proportion of patients with comorbidity had signs of pressure and volume overload, i.e. 73 (28,5 %) subjects in contrast with 2 patients (4,0%) ( $p < 0,0001$ ) with AH alone.

Hypertrophy of myocardium is considered a significant factor in cardiovascular risk and a manifestation of pathology of target organs in AH patients. The extent and severity of LV hypertrophy in patients with comorbidity is significantly greater than in patients with AH alone; significant role in

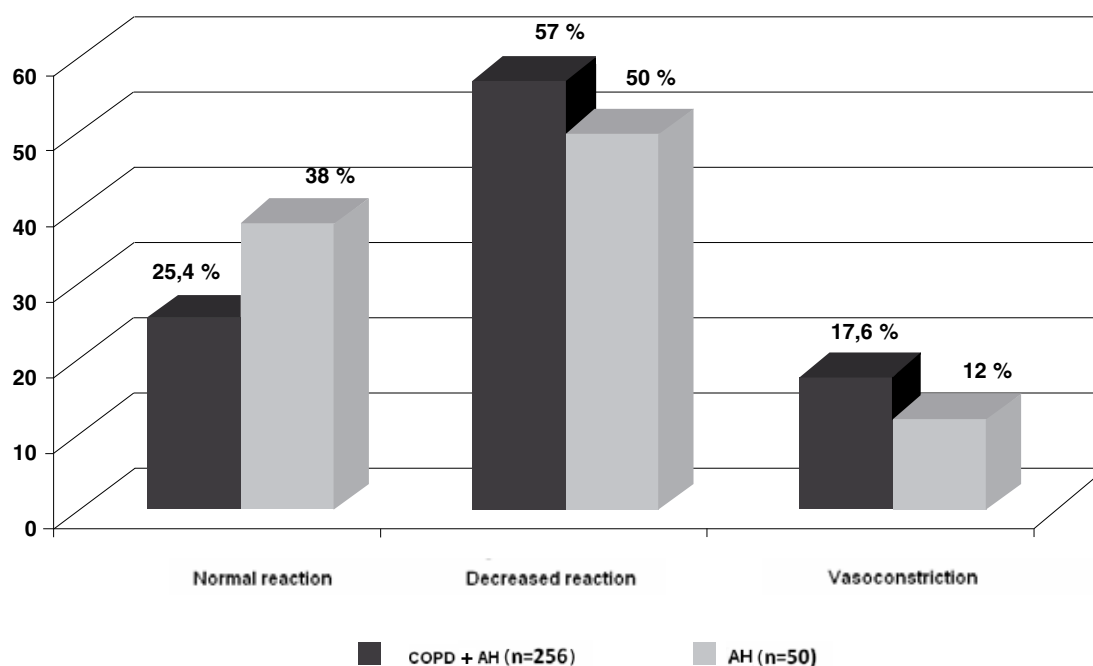


Figure 2. Distribution of patients depending on arterial vasoconstrictive function

development of these changes plays remodeling of right cardiac compartments due to dilatation and hypertrophy of RV.

Some clinical observations confirm the role of intima-media complex thickness of carotid arteries as a marker of systemic atherosclerosis and its growth is considered an independent risk factor for heart attack, stroke and sudden death

[5]. We noted the increase of thickness of intima-media in patients with comorbid disorders, although these changes were not significantly higher than those among patients with AH alone. This indicated additional adverse factor for cerebrovascular prognosis in patients with concomitant diseases. We also noted an increase in the number of patients with

Changes in remodeling of left and right ventricles and structural-morphological changes in carotid arteries in the subject groups			
Indicators	I group, COPD and AH (n = 256)	II group, AH (n = 50)	p
<i>Assessment of LV remodeling</i>			
Norm, %	10,5	6	0,26
Concentric hypertrophy of LV, %	55,5	64	0,020
Concentric remodeling of LV, %	18,8	22	0,040
Eccentric hypertrophy of LV, %	12,5	8	0,001
<i>Assessment of RV remodeling</i>			
Norm, %	0	50,1	0,0001
Pressure overload, %	25,8	16	0,002
Volume overload, %	45,7	30	0,040
Pressure and volume overload, %	28,5	4	0,0001
<i>Morphological vascular changes</i>			
IMCT, mm	1.18 ± 0.08	1,16 ± 0.07	0,42
Number of patients with constrictive narrowing of carotid arteries over 20%, abs, %	98 (38,2%)	18 (36%)	0,02

Note: The quantitative indicators are presented as (M ± m) – mean ± standard error of the average, the difference between groups is considered significant at p < 0,05.

Table 3

## Results of daily monitoring of blood pressure in subject groups

Indicators	Total subjects(n = 306)		
	COPD and AH (n = 256)	AH without COPD (n = 50)	p
Average SBP, 24-hours	135 (121; 140)	127 (126; 127)	0,017
Average DBP, 24-hours	78 (73; 83) <sup>#</sup>	77 (75; 80)	0,18
Average SBP, day-time	135 (122; 138) <sup>*#</sup>	126 (122; 129)	0,004
Average DBP, night-time	77 (71; 86) <sup>*#</sup>	77 (70; 81)	0,19
Time Index for SBP, 24-hours	45 (28; 53) <sup>*#</sup>	44 (30; 48)	0,31
Time Index for DBP, 24-hours	34 (23; 45) <sup>*#</sup>	25 (12; 37)	0,0003
Average 24-hour index	3,0 (0; 5.5) <sup>*#</sup>	-1,0 (-3.0; 9.0)	0,07
Rate of morning blood pressure growth	460 (152; 630) <sup>*#</sup>	100(4; 127)	0,0001

Note: The quantitative indicators are presented as Med (per 25; per 75) – median and inter-quartile space (25 and 75 percentile).

constrictive narrowing of carotid arteries, especially in patients with concomitant COPD and AH.

According to the results of daily ECG monitoring, we found that the patients from group I had significantly higher daily average systolic (SBP) and diastolic blood pressure (DBP), average day-time SBP, and average night-time DBP in contrast to patients with isolated course of diseases (Table 3).

It was found that comorbid COPD and AH patients had significantly higher time indexes for both over-the-day systolic and diastolic blood pressure in contrast to patients with isolated clinical diseases. The changes may indicate significant shift and stress in regulatory systems manifested in dysfunction of target organs. There were cases of significant increase in the rate of blood pressure growth, most often in patients with comorbid disorders and direct relationship with the AH severity. These results suggest a greater degree of hypertension impact on target organs and probably more severe and prognostically unfavorable course in patients with comorbidities.

## Conclusion

The analysis of clinical and instrumental data revealed that the presence of concomitant COPD may be considered an additional factor of cardiovascular risk in patients with comorbid pathology, as evidenced by the following information:

1. We found that 229 (89,4%) patients with comorbid COPD and AH had excessive weight, 100 (39,1%) patients were smokers with smoking index ( $25,2 \pm 2,84$ ) packs/year thus evidencing a high risk of cardiovascular events.

2. A portion of patients with diabetes mellitus among subjects with comorbid conditions was significantly higher – 61 patients (23,8%), 136 patients (53,1%) had various forms of CAD, thus allowing us to identify these patients according to the risk stratification scale as high risk of heart cardiovascular complications.

3. Dyslipidemia was diagnosed in 151 (59%) patients with a combination of COPD and AH; the levels of C-reactive protein,

an increase in endothelin-1 and decrease of nitrite/nitrate metabolites evidenced of the role of systemic inflammation in the development of functional disorders in this group of patients.

4. We noted an increase of thickness of intima-media complex in patients with comorbid conditions; despite the lack of significant changes in patients with AH alone, it was another adverse factor for cerebrovascular prognosis in patients with concomitant diseases.

5. The signs of endothelial dysfunction caused by violation of various mechanisms of regulation of vascular tonus was observed in 190 (74,6 %) patients with comorbid conditions, including metabolic and endothelial ones, thus confirming the role of endothelial dysfunction in this group of patients.

6. Patients with concomitant COPD and AH had significantly higher incidence of violation of remodeling of left and right ventricles, that greatly contributed to formation and progression of heart failure in this group of patients.

## References

1. Бичкова, С. А. Використання антигіпертензивних препаратів у хворих на хронічне обструктивне захворювання легень у поєднанні з артеріальною гіпертензією [Текст] / С. А. Бичкова // Науковий вісник НМУ ім. О. О. Богомольця. – 2009. – № 1. – С. 81–83.
2. Бойко, Д. М. Сучасні погляди на терапію хронічних обструктивних захворювань легень у поєднанні з есенціальною гіпертонічною хворобою [Текст] / Д. М. Бойко // Практична медицина. – 2006. – Т. XII, № 5. – С. 32–39.
3. Фещенко, Ю. И. Актуальные проблемы лечения больных хроническим обструктивным заболеванием легких [Текст] / Ю. И. Фещенко, Л. А. Яшина, А. Я. Дзюблик, В. К. Гаврисюк // Здоров'я України. – 2011. – № 2 (14). – С. 10–11.
4. Agustí, A. G. Systemic effects of chronic obstructive pulmonary disease [Text] / A. G. Agustí // Proc. Am. Thorac. Soc. – 2005. – Vol. 2. – P. 367–370.
5. Celli, B. R. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease [Text] / B. R. Celli, C. G. Cote, J. M. Marin // N. Engl. J. Med. – 2004. – № 350 (10). – P. 1005–1012.
6. Curkendall, S. M. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients [Text] / S. M. Curkendall, C. Deluise, J. K. Jones [et al.] // Ann. Epidemiol. – 2006. – Vol. 16. – P. 63–70.

7. Mannino, D. M. Global burden of COPD: risk factors, prevalence, and future trends [Text] / D. M. Mannino, S. A. Buist A. // Lancet. — 2007. — № 370 (9589). — P. 765–773.

8. Sin, D. D. Is COPD Really a cardiovascular disease? [Text] / D. D. Sin // Chest. — 2009. — № 136. — P. 329–330.

9. Torres, J. P. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients / J. P. Torres [et al.] // Eur. Respir. J. — 2006. — № 27(5). — P. 902–907.

#### СОЧЕТАНИЕ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЕГКИХ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ: ВЗАИМНОЕ ОТЯГОЩЕНИЕ И ВЫСОКИЙ РИСК СЕРДЕЧНО-СОСУДИСТЫХ ОСЛОЖНЕНИЙ

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##### Резюме

**Цель.** Установить распространенность факторов сердечно-сосудистого риска у пациентов с сочетанным течением хронического обструктивного заболевания легких (ХОЗЛ) и артериальной гипертензии (АГ), оценить влияние ХОЗЛ на течение АГ.

**Материалы и методы.** Обследовано 256 больных с сочетанным течением ХОЗЛ и АГ (I группа), средний возраст —  $(60,5 \pm 0,6)$  года, из них 158 (61,7 %) мужчин и 98 (38,3 %) женщин. Вторая (II) группа — 50 пациентов с АГ, без сопутствующих обструктивных заболеваний органов дыхания в анамнезе, средний возраст —  $(60,6 \pm 1,5)$  года, мужчин — 20 (40,0 %), женщин — 30 (60,0 %). Всем больным проведено суточное мониторирование ЭКГ, артериального давления, доплерэхокардиографию, определение уровня С-реактивного белка, эндотелина-1, метаболитов оксида азота.

**Результаты.** Среди обследованных I группы у 229 (89,4 %) диагностировано ожирение, 100 (39,1 %) пациентов курили, индекс пачко/лет составлял  $(25,2 \pm 2,84)$ , достоверно чаще диагностировали сахарный диабет — у 61 (23,8 %), разные формы ишемической болезни сердца — у 136 (53,1 %), дислипидемию — у 151 (59 %) пациента. У пациентов I группы имело место утолщение комплекса интима-медиа в отличие от пациентов II группы, что свидетельствует о дополнительном неблагоприятном факторе сердечно-сосудистого риска у больных с сопутствующей патологией.

**Выводы.** Сочетанное течение ХОЗЛ и АГ сопровождается взаимным отягощением и формированием факторов высокого сердечно-сосудистого риска.

**Ключевые слова:** хроническое обструктивное заболевание легких, артериальная гипертензия, высокий сердечно-сосудистый риск.

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#### COMBINED COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND HYPERTENSION: COMPLICATION AND HIGH RISK OF CARDIOVASCULAR COMPLICATIONS

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##### Summary

**Objective.** Establish the prevalence of risk factors for cardiovascular events in patients with COPD and in combination with hypertension, to assess the impact of COPD on the course of hypertension.

**Object and methods.** 256 patients who had a combination of COPD and hypertension, mean age  $(60,5 \pm 0,6)$  years, males were 158 (61,7 %), women — 98 (38,3 %) (group I). The second group consisted of 50 patients with hypertension without concomitant obstructive respiratory diseases in history, the average age of —  $(60,6 \pm 1,5)$  years, men — 20 (40,0 %), women — 30 (60,0 %). All patients underwent daily monitoring of ECG, blood pressure, Doppler echocardiography, determination of C-reactive protein, endothelin -1, and nitric oxide metabolites.

**Results.** Of surveys and group 229 (89,4 %) showed overweight, 100 (39,1 %) patients smoked index a pack / years was  $(25,2 \pm 2,84)$ , significantly more often diagnosed with diabetes — in 61 patients (23,8 %), and 136 (53,1 %) — various forms of coronary artery disease in 151 (59 %) patients dyslipidemia, marked increase in the thickness of the intima — media complex in contrast to the second group of patients, indicating that additional adverse factor cerebrovascular prognosis in patients with concomitant diseases.

**Conclusion.** Combined course of COPD and hypertension are associated with mutual encumbrance and additional cardiovascular risk.

**Key words:** chronic obstructive pulmonary disease, hypertension, overall cardiovascular risk factors.

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