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# SOME PECULIARITIES OF SEASONAL DEVIATIONS IN INDICATORS OF LIPID PEROXIDATION AND ANTIOXIDANT PROTECTION IN PATIENTS WITH COMPENSATED CHRONIC COR PULMONALE OF BRONCHO-PULMONARY GENESIS AND IN THE CONDITIONS OF ITS COMORBIDITY WITH STABLE CORONARY HEART DISEASE

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*It is known that chronic obstructive pulmonary disease (COPD) and cardiovascular diseases have common pathophysiological mechanisms that are closely related to oxidative stress. In order to research the peculiarities of the state of lipid peroxidation (LPO), the antioxidant defense (AOD) system and their seasonal deviations in patients with compensated chronic cor pulmonale (CCP) of broncho-pulmonary genesis in conditions of comorbidity with stable coronary heart disease (CHD), a study and analysis of LPO indicators (diene conjugates, malondialdehyde), the AOD system (erythrocytes peroxide hemolysis test, superoxide dismutase, catalase, ceruloplasmin) in 52 patients with COPD and compensated CCP, among whom 32 patients had comorbid stable CHD (the main group), were carried out; 20 patients with isolated pathology (COPD with compensated CCP) formed the comparative group. The research was carried out during summer-autumn and winter-spring seasons. It was established that in patients of the comparative group the activation of LPO processes is observed, while the intensity of their seasonal fluctuations is minimal. Patients of the main group are characterized by a higher activity of LPO processes, which is combined with a decrease in the activity of the enzyme link of the AOD system, and an increase in the intensity of LPO with signs of depletion of the functional activity of key enzymes of the AOD system is observed during winter-spring period of the year; this result implies the need to use a differentiated approach in the complex treatment of these patients to optimize the antioxidant status.*

***Key words:*** *lipid peroxidation, antioxidant defense, chronic cor pulmonale, stable coronary heart disease.*

**Connection of the publication with planned research works.**

This work is a fragment of the research work of the Department of Propaedeutics to Internal Medicine of Poltava State Medical University, “Peculiarities of the course of cardiovascular pathology in patients of different age categories, depending on the presence of components of the metabolic syndrome and comorbid conditions, ways of correcting the revealed disorders and prevention” (state registration number 0119U102864).

**Introduction.**

Chronic obstructive pulmonary disease (COPD) is a problem, the relevance of which is rapidly increasing over the world because the number of patients with this disease is constantly increasing [1]. According to the forecasts of the World Health Organization experts, the current decade will be marked by an increase in the incidence of this pathology by another 30%, if certain prevalence measures are not taken [2]. COPD is the most important cause of the development of chronic cor pulmonale (CCP), and the presence of CCP is a factor that determines the development of adverse events, besides in the future COPD remains the third leading cause of death in the world by mortality rates [3].

Comorbid pathology and, first of all, cardiovascular diseases, adversely affect the course of COPD and the works of recent years also emphasize this fact [4, 5]. Existing cardiovascular diseases are the cause of more than half of hospitalization and fatal outcomes in patients with COPD [6]. A systematic review of the Global Burden of Disease Study, which was carried out in 2017, found that the most common cause of early death from COPD is coronary heart disease (CHD) – more than one million cases worldwide [7]. The analysis of literature data also indicates a high frequency of the combination of COPD and CHD, which varies from 20 to 60% depending on the age and duration of the disease [8, 9]. The high degree of such comorbidity is explained, first of all, by the presence of common risk factors and links of the pathogenesis of diseases, however, a certain number of them and possible mechanisms of “mutual burden” need to be clarified [10]. The existing problem, thus, provides for more detailed study of various mechanisms involved in the formation of this comorbid pathology, both in cases with disorders of systemic cardiohemodynamics and without them.

It is known that COPD and cardiovascular diseases have common pathophysiological mechanisms that are closely related to oxidative stress [11]. Activation of the processes of lipid peroxidation (LPO) is a universal response of the body to stress, during which it becomes possible to have imbalance between the production of free radicals and the effectiveness of the antioxidant defense (AOD) system. The balance between these components keeps the state of peroxidation at a level that prevents the development of oxidative stress [12, 13], and its shift plays a significant role in the pathogenesis of many diseases including both COPD [14, 15] and CHD [16, 17]. It is reported that in the case of comorbidity of COPD and cardiovascular diseases, the above imbalance increases local inflammatory processes, has a systemic effect, contributes to the development of concomitant diseases associated with COPD, and worsens the state of the cardiovascular system [18].

Despite the fact that combination of COPD and CHD is of great interest to both researchers and practitioners,

the study of the state of lipid peroxidation and the antioxidant defense system in patients with compensated chronic cor pulmonale of broncho-pulmonary genesis in conditions of comorbidity with coronary heart disease, taking into account seasonality, is not numerous. It became the basis for carrying out this work.

**The aim of the study.**

To investigate, analyze and determine the peculiarities of the state of lipid peroxidation, the antioxidant defense system and their seasonal deviations in patients with compensated CCP of broncho-pulmonary genesis in conditions of comorbidity with stable CHD.

**Object and research methods.**

In order to solve the set aim, the study and analysis of indicators of LPO and the AOD were carried out in 52 patients with COPD [19, 20, 21] and compensated CCP [22] (females – 22, males – 30, the mean age – 54,4±2,2 years), among whom 32 patients had comorbid CHD (angina pectoris, functional class II-III, postinfarction and/or atherosclerotic cardiosclerosis) [23] (the main group); 20 patients with isolated pathology (COPD with compensated CCP) formed the comparative group. The representatives of the both groups were of the same sex, age and duration of the disease; the carrying out treatment of both CCP of broncho-pulmonary genesis and CHD met the requirements of the unified protocols. The study was conducted in accordance with the principles of the Helsinki Declaration on the Protection of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and the provisions of the relevant laws of Ukraine. The study protocol was approved by the Local Ethics Committee for all participants. Written informed consent was obtained from all patients who participated in the study.

The state of LPO was determined by the content of malondialdehyde (MDA) and diene conjugates (DC) in the blood serum [24], activity of AOD system – by erythrocytes peroxide hemolysis test (EPHT), as a marker of tocopherol content [25], the level of ceruloplasmin (CP) [26], the activity of superoxide dismutase (SOD) and catalase (CAT) enzymes in the blood [27]; research was carried out during summer-autumn and winter-spring seasons. The obtained research results were compared between groups of patients and also with the indices of practically healthy individuals (n=10) who were of the same sex and age.

Statistical analysis of the results was carried out by parametric statistics. Student's t-test was used to estimate the significance of differences. The difference of indices was significant in case of $p<0.05$.

**Research results and their discussion.**

The results of the study, carried out during the summer-autumn season, revealed **(figure 1)** that in patients with compensated CCP of broncho-pulmonary genesis the EPHT was 4.2±0.4%; it was 1,8 times ($p<0.02$) as large as among control group (2.3±0.4%). An increase in the content of CP in the blood was observed – up to 96.0±1.6 mg/l (in the group of practically healthy individuals – 84.5±1.2 mg/l; $p<0.001$). The level of intermediate products of lipid peroxidation (DC) in these patients was 46.8±1.2 µmol/l, it was 1.1 times ($p<0.05$) as large as indicator of the control group (42.4±1.0 µmol/l), while the content of the final product (MDA) was 4.4±0.3 µmol/l (in practically healthy individuals – 4.3±0.6 µmol/l); the activity of enzymes of the AOD system (SOD and CAT) in patients with compensated CCP was also within the control values.

Changes of the LPO indicators and enzymes of AOD system in patients with comorbid pathology were more significant – EPHT increased to 5.8±0.5%, and CP content to 128.5±1.3 mg/l, which exceeded control indicators, respectively, by 2.5 ($p<0.01$) and 1.4 times ($p<0.05$). A significant (compared to the group of practically healthy individuals) increase of the DC content – up to 55.6±2.1 µmol/l (by 1.3 times, $p<0.01$) and a significant decrease of SOD activity – up to 0.6±0.002 UA/ml (it was lower than the indicator of the control group (1.0±0.2 UA/ml) by 40%, $p<0.01$) were observed, while trends of decreasing CAT activity and increasing (by 1.3 times) MDA content were observed (up to 5.9±0.8 µmol/l). It should be emphasized that in patients with comorbid pathology, compared to patients with compensated CCP, EPHT was 1.4 times higher ($p<0.05$), the level of CP was 1.3 times higher ($p<0.001$), the content of DC – by 1.2 times ($p<0.05$), MDA – by 1.3 times, while the activity of SOD, compared to patients with compensated CCP (0.9±0.003 UA/ml), was reduced by a third ($p<0.001$), and there was also a tendency to decrease the activity of CAT.

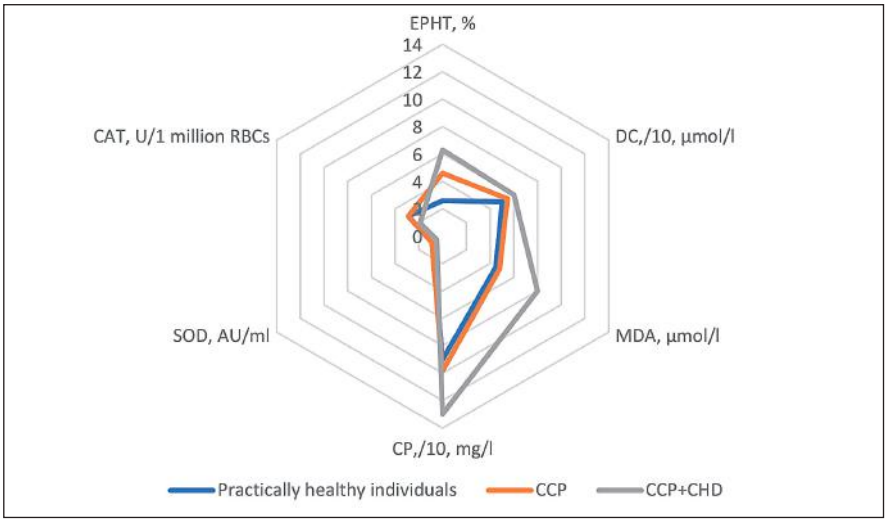


**Figure 1 – Indices of lipid peroxidation and antioxidant protection in patients with compensated CCP and in conditions of comorbidity with CHD during summer-autumn season.**

It should be emphasized that the pathogenesis of COPD and its most common accompanied cardiovascular diseases, among which CHD has a «rightful» place, is associated with common genetic factors, environmental risk factors, lifestyle, as well as numerous pathophysiological processes, including systemic inflammation, endothelial dysfunction and accelerated aging [18, 28]. It is noted that they have a close connection with oxidative stress, while, on the one hand, its activation occurs under the influence of exogenous and endogenous oxidative radicals, and on the other, conditions are formed for further oxidative stress, which induces the

production of reactive oxygen species and weakens antioxidant defense mechanisms [18]. The data we obtained, which indicated the activation of LPO in patients with compensated CCP of broncho-pulmonary genesis, also indicated that in the conditions of combination CCP with CHD there was a significant increase in the activity of LPO processes with signs of functional depletion of the enzymatic link of the AOD system, which could be a reflection of the existing "mutual burden" of combined pathology [29].

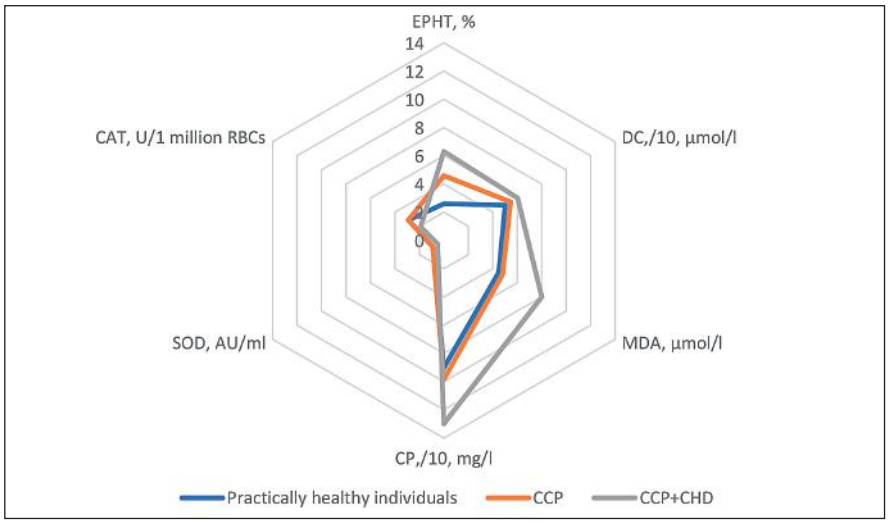


**Figure 2 – Indices of lipid peroxidation and antioxidant protection in patients with compensated CCP and in conditions of comorbidity with CHD during winter-spring season.**

The study of the state of LPO and AOD system during the winter-spring season revealed **(figure 2)** that in patients with compensated CCP of broncho-pulmonary genesis, in comparison with practically healthy individuals, there were changes, the direction of which was similar to those during the summer-autumn period. Thus, compared to the control, the EPHT indicator (by 1.8 times) (4.6±0.3% vs. 2.6±0.4%; p<0.01), the level of CP (98.4±1.2 mg/ml vs. 90.2±1.3 mg/l; p<0.002), DC blood content (54.6±1.2 µmol/l vs. 50.2±1.1 µmol/l; p<0.05) were significantly increased, while the content of the final product of LPO and the activity of enzymes of the AOD system didn't have reliability of the difference with the indicators of the control group. The changes in indicators of LPO and AOD system in patients with compensated CCP with comorbid CHD turned out to be quite interesting, and not only in comparison with practically healthy individuals, but also with patients with compensated CCP. So, the EPHT indicator was 6.3±0.6%, which was higher than this indicator of the control group and patients with CCP, respectively, by 2.4 (p<0.01) and 1.4 (p<0.05) times; the MDA content was 8.0±0.7 µmol/l and exceeded this indicator of the control group (4.5±0.7 µmol/l) by 1.8 times (p<0.02) and by 1.7 times – of the patients with CCP(4.8±0.8 µmol/l; p<0.01). The content of CP also increased significantly – up to 129.8±1.4 mg/l, which was 1,4 times (p<0.001) as large as among practically healthy individuals and 1.3 times as large as among patients with CCP (p<0.001), which could also be a reflection of a more significant intensification of inflammatory processes in conditions of comorbidity [30]. A 1.5-fold decrease in CAT activity and a 1.8-fold decrease in SOD activity (0.5±0.002 UA/ml) compared to practically healthy, as well as patients with compensated CCP (p<0.001 in both cases) were the peculiarities of changes in the activity of key enzymes of the AOD system in patients with compensated CCP in combination with stable CHD.

The analysis of seasonal changes in the activity of LPO and the AOD system indicators revealed that their dynamics were minimal in patients with CCP, and the most significant seasonal changes during the winter-spring season were observed in patients with comorbid pathology – a reduction of SOD (by 1.2 times) and CAT (by 1.5 times) and an increase of the final product of peroxidation (by 1,4 times) were noted. This results to some extent are compatible with the data of other studies [31] and should be considered as a prerequisite for the active use of therapeutic opportunities to restore the oxidative balance [32, 33].

**Conclusions.**

In patients with compensated CCP of broncho-pulmonary genesis the activation of lipoperoxidation processes is observed, while the intensity of their seasonal fluctuations is minimal.

Patients with compensated CCP of broncho-pulmonary genesis in combination with stable CHD are characterized by a higher activity of LPO processes, which is combined with a decrease in the activity of the enzyme link of the AOD system, and an increase in the intensity of LPO with signs of depletion of the functional activity of key enzymes of the AOD system is observed during winter-spring period of the year.

The seasonality of the revealed changes in the activity of LPO processes and the AOD system in patients with CCP of broncho-pulmonary genesis with comorbid stable CHD and the presence of seasonal deviation implies the need to use a differentiated approach in the complex treatment of patients of this category with the use of therapeutic measures to optimize the antioxidant status.

**Prospects for further research.**

Taking into account the data obtained in the study, in the future it is appropriate to study the peculiarities of changes in LPO and AOD indicators in patients with decompensated CCP of bronchopulmonary genesis and comorbid CAD.

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## ДЕЯКІ ОСОБЛИВОСТІ СЕЗОННИХ ДЕВІАЦІЙ ПОКАЗНИКІВ ПЕРЕКИСНОГО ОКИСЛЕННЯ ЛІПІДІВ ТА АНТИОКСИДАНТНОГО ЗАХИСТУ У ХВОРИХ НА КОМПЕНСОВАНЕ ХРОНІЧНЕ ЛЕГЕНЕВЕ СЕРЦЕ БРОНХО-ЛЕГЕНЕВОГО ГЕНЕЗУ ТА В УМОВАХ ЙОГО КОМОРБІДНОСТІ ЗІ СТАБІЛЬНОЮ ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ

**Петров Є. Є., Бурмак Ю. Г., Іваницька Т. А., Трибрат Т. А., Савчук Т. А.**

**Резюме.** Аналіз даних літератури свідчить про високу частоту поєднання хронічного обструктивного захворювання легень (ХОЗЛ) та ішемічної хвороби серця (ІХС). Відомо, що ХОЗЛ та серцево-судинні захворювання мають спільні патофізіологічні механізми, які щільно пов'язані з окисним стресом. Активація процесів перекисного окислення ліпідів (ПОЛ) є універсальною реакцією організму на стрес-вплив, впродовж якої є можливим наявність порушень балансу між продукцією вільних радикалів та дієспроможністю системи антиоксидантного захисту (АОЗ). З метою дослідження особливостей стану ПОЛ, системи АОЗ та їх сезонних девіацій у хворих на компенсоване хронічне легеневе серце (ХЛС) бронхо-легеневого ґенезу в умовах коморбідності зі стабільною ІХС проведено вивчення та аналіз показників ПОЛ (дієнові кон'югати, малоновий діальдегід) та системи АОЗ (перекисний гемоліз еритроцитів, супероксиддисмутаза, каталаза, церулоплазмін) у 52 хворих на ХОЗЛ із компенсованим ХЛС, серед яких 32 хворих мали коморбідну стабільну ІХС (стенокардія на-

пруги, функціональний клас II-III, післяінфарктний та/або атеросклеротичний кардіосклероз) (основна група досліджених); 20 хворих з ізольованою патологією (ХОЗЛ із компенсованим ХЛС) склали групу зіставлення. Дослідження проводили в літньо-осінню та зимово-весняну пори року. Отримані результати порівнювались між групами хворих та з показниками практично здорових осіб, які мали ідентичну обстеженим хворим статево-вікову структуру. Встановлено, що у хворих на компенсоване ХЛС бронхо-легеневого ґенезу спостерігається активація процесів ліпопероксидації, при цьому інтенсивність їх сезонних коливань є мінімальною. Хворим на компенсоване ХЛС бронхо-легеневого генезу у поєднанні зі стабільною ІХС притаманна більш висока активність процесів ПОЛ, що поєднується зі зниженням активності ферментної ланки системи АОЗ, а підвищення інтенсивності ПОЛ із ознаками виснаженням функціональної активності ключових ферментів системи АОЗ спостерігається у зимово-весняний період року. Сезонність виявлених змін активності процесів ПОЛ та системи АОЗ у хворих на ХЛС бронхо-легеневого ґенезу із коморбідною стабільною ІХС та наявність сезонної девіації передбачає необхідність використання диференційованого підходу у комплексному лікуванні хворих вказаної категорії із використанням терапевтичних заходів з оптимізації антиоксидантного статусу.

**Ключові слова:** перекисне окислення ліпідів, антиоксидантний захист, хронічне легеневе серце, стабільна ішемічна хвороба серця

## SOME PECULIARITIES OF SEASONAL DEVIATIONS IN INDICATORS OF LIPID PEROXIDATION AND ANTIOXIDANT PROTECTION IN PATIENTS WITH COMPENSATED CHRONIC COR PULMONALE OF BRONCHO-PULMONARY GENESIS AND IN THE CONDITIONS OF ITS COMORBIDITY WITH STABLE CORONARY HEART DISEASE

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**Abstract.** The analysis of literature data indicates a high frequency of the combination of chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD). It is known that COPD and cardiovascular diseases have common pathophysiological mechanisms that are closely related to oxidative stress. Activation of the processes of lipid peroxidation (LPO) is a universal response of the body to stress, during which it becomes possible to have imbalance between the production of free radicals and the effectiveness of the antioxidant defense (AOD) system. In order to research the peculiarities of the state of LPO, the AOD system and their seasonal deviations in patients with compensated chronic cor pulmonale (CCP) of broncho-pulmonary genesis in conditions of comorbidity with stable CHD, a study and analysis of LPO indicators (diene conjugates, malondialdehyde), the AOD system (erythrocytes peroxide hemolysis test, superoxide dismutase, catalase, ceruloplasmin) in 52 patients with COPD and compensated CCP, among whom 32 patients had comorbid stable CHD (angina pectoris, functional class II-III, postinfarction and/or atherosclerotic cardiosclerosis) (the main group) were carried out; 20 patients with isolated pathology (COPD with compensated CCP) formed the comparative group. The research was carried out during summer-autumn and winter-spring seasons. The obtained research results were compared between groups of patients and also with the indices of practically healthy individuals who were of the same sex and age. It was established that patients with compensated CCP of broncho-pulmonary genesis the activation of lipoperoxidation processes is observed, while the intensity of their seasonal fluctuations is minimal. Patients with compensated CCP of broncho-pulmonary genesis in combination with stable CHD are characterized by a higher activity of LPO processes, which is combined with a decrease in the activity of the enzyme link of the AOD system, and an increase in the intensity of LPO with signs of depletion of the functional activity of key enzymes of the AOD system is observed during winter-spring period of the year. The seasonality of the revealed changes in the activity of LPO processes and the AOD system in patients with CCP of broncho-pulmonary genesis with comorbid stable CHD and the presence of seasonal deviation implies the need to use a differentiated approach in the complex treatment of patients of this category with the use of therapeutic measures to optimize the antioxidant status.

**Key words:** lipid peroxidation, antioxidant defense, chronic cor pulmonale, stable coronary heart disease.

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