

пізніх стадіях перетворюється на діастолічну серцеву недостатність з наступним приєднанням систолічної серцевої недостатності. У шахтарів з гіпертонічним серцем структурно-функціональний статус правого шлуночка зазнає ранніх порушень, що виявляється за діастолічної дисфункції.

Ключові слова: артеріальна гіпертензія, гіпертензивне серце, ремоделювання лівого шлуночка.

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діастоліческая дисфункція левого желудочка, которая на более поздних стадиях превращается в диастолическую сердечную недостаточность с последующим присоединением систолической сердечной недостаточности. У шахтеров с гипертоническим сердцем структурно-функциональный статус правого желудочка испытывает ранние нарушения, проявляющиеся диастолической дисфункцией.

Ключевые слова: артериальная гипертензия, гипертензивное сердце, ремоделирование левого желудочка.

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PATHOGENETIC EFFECTS IN THE TREATMENT OF COMBINED CARDIORESPIRATORY PATHOLOGY

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Study of the possibility to correct endothelial dysfunction (ED), structural changes in peripheral arteries and synthesis of metabolic-waste products of nitric oxide (NO) (nitrites NO_2^- / nitrates NO_3^-) by means of including the combination of roflumilast and quercetin to the background therapy has been investigated. In 6 months, the use of complex therapy, in contrast to the background one, has resulted in a statistically significant increase of the initial rate by 18.76% from (0.61 ± 0.04) m/s to (0.75 ± 0.04) m/s ($t=2.47$; $p<0.05$) and in a statistically significant decrease of the initial diameter of a brachial artery to 3.74 ± 0.28 mm ($t=2.49$; $p<0.05$). Administration of complex therapy after 6 months has showed that the concentration of NO metabolites in the blood has gone up 1.3 times, up to 10.35 ± 1.89 $\mu\text{mole/l}$ ($t=1.00$; $p>0.1$) with the norm of 12.05 ± 2.11 $\mu\text{mole/l}$. Administration of complex therapy for patients with a severe stage of chronic obstructive pulmonary disease (COPD) in an exacerbation phase accompanied with a stable coronary artery disease and stable effort angina (SCAD SEA) of the 2nd FC helps restore endothelial function, improves peripheral arterial structural changes and has a stimulating effect on the synthesis of NO.

Key words: stable coronary artery disease, chronic obstructive pulmonary disease, endothelial dysfunction, oxidative stress.

The study is a fragment of the research project "Clinical and immunological aspects of the internal organs major diseases course and their correction", state registration No. 0114U002040.

It is well-known nowadays, that oxidative stress is the most important pathogenetic factor of a wide range of disorders, including cardiovascular diseases, transient ischemic attack, COPD, diabetes mellitus etc. Moreover, it is oxidative stress that initiates the development and progression of mitochondrial diseases, bronchopulmonary dysplasia, atopy and many other conditions [1].

According to contemporary views, oxidative stress, regarded as an imbalance between the production and degradation of free oxygen forms, plays an important role in many physiological processes (tissue growth and maturation, cell differentiation, antineoplastic activity, natural cytotoxicity, immune response, repair) and basic pathological conditions such as blood clotting, inflammation, apoptosis etc. [7-8]. In addition, the main biological role of oxidative stress is renewal of cell membranes, membrane-associated receptors, enzymes, signaling molecules, ionic pumps [1] and accumulation of free radicals that lead to the oxidation of unsaturated fatty acids in cell membranes, proteins and DNA as well as the formation of polar permeable channels, which increases passive permeability of the membrane for Ca^{2+} ions, the excess of which is deposited in mitochondria, inducing its dysfunction [5].

As a result of this process, a deficiency of energy-rich products occurs, which is accompanied by the activation of peroxidation, which reflects different by severity damages of target organs through the process of ischemia/reperfusion, apoptosis/necrosis. It is assumed that oxidative stress significantly reduces the bioavailability of NO [10], which is responsible for adequate vasodilatation, both through a direct suppression of its products and by increasing the production of superoxide and peroxide anions [3]. The latter can react rapidly with NO and form a by-product peroxynitrite (ONOO⁻), which is modified to peroxynitric acid, which in its turn forms a hydroxyl radical (O⁻) [4]. This reaction forms the basis for the processes of lipid oxidation of vascular wall membranes and of blood corpuscles. Moreover, accumulation of endoperoxides in the endothelium due to mononuclear angiotensin 2 mediated activation leads to vascular remodeling; and the concomitant activation of the local renin-angiotensin system through the mobilization of cellular adhesion molecules determines the increasing anticoagulation potential [9].

Thus, achievement of adequate control over the activity of activators and counterregulators of oxidative stress could become a significant breakthrough in the prevention and treatment of numerous diseases, particularly COPD and cardiovascular diseases. Previously conducted studies have proved that expression of enzymatic and non-enzymatic prooxidant systems is substantially modified due to the influence of traditional risk factors of cardiovascular diseases or COPD [2].

The purpose of the work was to study the possibility to correct endothelial dysfunction (ED), structural changes in peripheral arteries and synthesis of metabolic-waste products of nitric oxide (NO) (nitrites NO_2^- / nitrates NO_3^-) by means of including the combination of roflumilast and quercetin to the background therapy for patients suffering from COPD in an exacerbation phase accompanied with SCAD SEA of the 2nd FC.

Materials and methods. The object of the study was a group of 44 patients (average age 59.13 ± 14.3) with verified diagnoses of severe COPD in an exacerbation phase accompanied with SCAD SEA of the 1st – 2nd FC. There were 38 men (86.36%) and 6 women (14.64%). It should be noted that prevailing number of men with the exacerbation of COPD were 60-70 years old (52.3%), less of them were 50-60 years old (19.6%) and the least number of men were over 70 (15,2 %). Among women, patients aged 60-70 (42.9%) were predominant, and women over 70 (28.6%) were less in number.

The diagnosis and severity of COPD was made according to the Order of the Ministry of Healthcare of Ukraine No. 555 as well as terms and conditions formulated in GOLD document (Global Initiative for Chronic Obstructive Lung Disease) 2016 [6]. Clinical and instrumental characteristics of functional disorders and structural changes in the heart were diagnosed according to the “Recommendation on treatment of stable coronary heart disease” of the European Cardiology Society and National Adapted Clinical Guideline “Stable ischemic heart disease” (Ministry of Healthcare of Ukraine, 2016).

NO levels were measured by identification of nitrites (NO_2^-) and nitrates (NO_3^-), i.e. NO metabolic products in $\mu\text{mole/l}$, by means of liquid chromatography method performed by Shimadzu apparatus with a UV detector using Griess reagent following a standard method.

A systemic function of the endothelium was investigated in the morning before the intake of antianginal drugs. All patients were made two subsequent tests: reactive hyperemia test (RH) and exercise tolerance test (ET). The period of time between testing was (20 ± 5) minutes, which is sufficient for the brachial artery (BA) to restore its original state after RH test. RH test was made according to the method of D. Celermajer et al. modified by O.V. Ivanova et al. To obtain an image of a right BA, measurements of its diameter and blood flow rates we used a device called Toshiba SSH-160A (Japan), in the mode of two-dimensional ultrasonic scanning with a 7 MHz linear sensor. On the basis of findings, the percentage of BA expansion in response to RH and ET was calculated.

With the help of ultrasonic dopplerography of the peripheral arteries, we measured the thickness of the intima-media complex (IMC), presence and localization of atheromatosis and the diameter of vessels in the region of bifurcation of common and internal carotid arteries on the right and left sides by means of “Toshiba SSH-160A” (Japan) 5.5-7.5 MHz linear sensor in real-time mode according to the method of D. Celermajer et al. (1992). The state of IMC was evaluated according to the following parameters: echogenicity, thickness (TIM), diameter (D), surface form, homogeneity, TIM/D index (integral indicator of vascular wall remodeling characterizing the degree of intima-media complex thickening). In addition, according to the method of E.B. Cooperberg et al., parameters of blood flow rates were defined: pulsatile (PI) and resistive (RI) indices that indicate hemodynamic disorders.

Depending on the applied therapy administered by means of randomization, taking into account clinical symptoms and findings of physical, laboratory and functional cardiac and pulmonary examination, patients were split into 2 groups: index group ($n = 26$) and experimental group ($n = 18$). Patients of the index group were administered background therapy of COPD and traditional anti-ischemic therapy according to current clinical agreements. Patients of the experimental group were prescribed a combination of roflumilast and quercetin in addition to the standard treatment of COPD and SCAD. The control group included 28 AHP (apparently healthy people) at the age of 38-49, whose average age was 46.3 ± 2.4 years old. Reassessment of endothelial function, structural changes of a BA and end products of NO metabolism (nitrites NO_2^- / nitrates NO_3^-) was carried out in 6 months – 1 year after treatment.

Statistical analysis of the findings was carried out by means of the software Microsoft Excel spreadsheet and statistical software package “Statistica v. 10.0 StatSoft” (USA).

Results of the study and their discussion. Average values of some indices of endothelial function, structural state and local haemodynamics of the BA before and after 6 months of standard and complex therapy in specified groups of patients are given in table 1.

As it can be seen from the data provided, the background therapy of COPD and SCAD SEA of the 1st – 2nd FC had a less pronounced effect compared with the complex therapy, since there were no significant changes in any index characterizing the endothelial function of a BA in the index group after treatment. Apparently this is due to expressive structural changes of the BA at this stage of the disease (dystrophy, sclerosis, thrombosis) or to insufficient therapeutic effect of the administered therapy.

Alternately, the use of complex therapy was accompanied with a significant decrease of the initial diameter of a BA in 6 months up to (3.74 ± 0.28) mm (t=2.49; p<0.05).

The initial rate of blood flow after 6 months of background supportive therapy has increased insufficiently only by 9.27% to (0.72 ± 0.44) m/s (t=0.97; p>0.1), while in the experimental group the initial blood flow rate after 6 months of intensive supportive therapy has increased significantly by 18.76% (0.61 ± 0.04) m/s to (0.75 ± 0.04) m/s (t=2.47; p<0.05).

Table 1

Indices of endothelial function and BA in patients suffering from severe COPD in an exacerbation phase accompanied by SCAD SEA of the 1st – 2nd FC before and after the treatment

Indices	Groups of patients			
	Index group, (n=26)		Experimental group, (n=18)	
	Before treatment	After treatment	Before treatment	After treatment
Initial diameter of BA, mm	4.38±0.12	4.20±0.28	4.42±0.11	3.74±0.28●
EDVD (endothelium-dependent vasodilation), %	3.90±0.12	4.34±0.40	2.45±0.20	5.08±0.18●
EIVD (endothelium-independent vasodilation), %	4.14±1.32	4.30±2.42	1.03±0.16	4.75±0.41●●●
Initial blood flow rate, m/s	0.65±0.06	0.72±0.04	0.61±0.04	0.75±0.04●

Note: statistical validity of the difference between index values: * – of the index group before and after the treatment: * – (p<0.05); ** – (p<0.01); *** – (p<0.001); ● – of the experimental group before and after the treatment: ● – (p<0.05); ●● – (p<0.01); ●●● – (p<0.001); ■ – of the index and experimental groups after the treatment: ■ – (p<0.05); ■■ – (p<0.01); ■■■ – (p<0.001).

On discharge from the in-patient department, mean values of the endothelium-dependent vasodilatation (EDVD) in patients of the index group increased insufficiently from (3.90 ± 0.12) % to (4.32 ± 0.32) % and only to (4.34 ± 0.40) % after 6 months of observation and treatment on an outpatient basis (t=1.23 and 1.03, respectively, p>0.1 for both indices). Conversely, patients of the experimental group have shown a significant increase in mean values of EDVD from (2.45 ± 0.20) % to (3.01 ± 0.13) % at the end of in-patient treatment and to (5.08 ± 0.18) % after 6 months of intensive supportive therapy (t=2.17; p<0.05). It should be clarified that the values of EDVD indices of the index and experimental groups in 6 months – 1 year were significantly different (t=3.79; p<0.01).

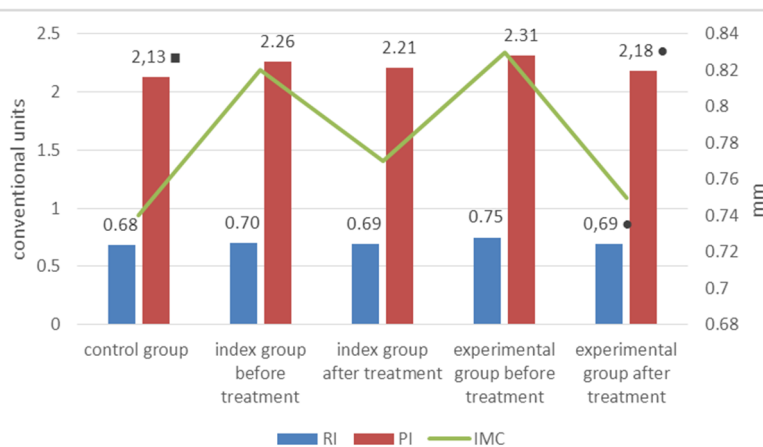


Fig. 1. Indices of the structural and functional state of vessels in the region of bifurcation of general and internal carotid arteries on the right and left sides in patients suffering from COPD in an exacerbation phase accompanied with SCAD before and after the treatment: * – statistical significance of the difference between the indices in the experimental group before and after the treatment: * – (p<0.05); ** – (p<0.01); *** – (p<0.001); ● – statistical significance of the difference between the indices in the index group before and after the treatment: ● – (p<0.05); ●● – (p<0.01); ●●● – (p<0.001); ■ – statistical significance of the difference between the indices in the experimental and index groups after the treatment: ■ – (p<0.05); ■■ – (p<0.01); ■■■ – (p<0.001).

vessels in the region of bifurcation of general and internal carotid arteries on the right and left sides, differences in the indices of structural changes depending on the choice of therapy have been revealed (fig. 1).

According to the study findings, a significant increase in the endothelium-independent vasodilatation (EDVD) in patients of the experimental group after 6 months of intensive supportive therapy to (4.75 ± 0.41) % (t=8.45; p<0.001) has been established. At the same time, the study of these indices of patients from the index group indicates an insignificant improvement of EIVD after half a year of background supportive therapy. Thus, a combination of roflumilast and quercetin, which possess anti-inflammatory and antioxidant properties, considerably improves the endothelial function of peripheral arteries.

With further study of the structural and functional state of

Thus, in patients of the index group after six months of the background therapy, IMC index has appeared to be only 1.06 times lower than the input data and has not reached the level of the AHP group ($t=0.15$; $p>0.1$). The IMC index for patients in the experimental group has reached (0.75 ± 0.18) mm, which is considerably lower than the index before treatment ($t=0.31$; $p>0.1$). In patients of the index group the index of RI has reached (0.69 ± 0.01) c.u. (conventional unit), which is 1.04 times higher than in the AHP group ($t=0.71$; $p>0.1$), while in the experimental group, the data has showed a significant decrease in the RI to (0.69 ± 0.02) c.u. ($t=2.12$; $p<0.05$). The value of pulsation index in patients of the study groups at the onset of inpatient treatment was higher than the control values, while in six months of supportive therapy a decreasing tendency of this index ($t=1.77$; $p<0.1$) in the index group has been observed as well as the experimental group has revealed significant changes ($t=2.91$; $p<0.05$). On admission to inpatient department, a decrease in the level of NO metabolites in the serum indicated a significant malfunction of NO metabolism in patients from both groups (table 2).

Table 2

Mean values of NO metabolite indices ($\mu\text{mol/l}$) in patients suffering from COPD of the 3rd severity level in an exacerbation phase accompanied with SCAD SEA of the 1st – 2nd FC before and after the treatment

Time of investigation	Control group, (n=28)	Patients with combined CPP (cardiorespiratory pathology), (n=44)			
		Index group, n=26		Experimental group, (n=18)	
		Before treatment	After treatment	Before treatment	After treatment
After 6 months of inpatient treatment	12.05±2.11	8.22±0.98	8.95±1.26	8.22±0.98	10.35±1.89

Note: statistical validity of the difference between index values: * – of the index group before and after the treatment: * – ($p<0.05$); ** – ($p<0.01$); *** – ($p<0.001$); ● – of the experimental group before and after the treatment: ● – ($p<0.05$); ●● – ($p<0.01$); ●●● – ($p<0.001$); ■ – of the index and experimental groups after the treatment: ■ – ($p<0.05$); ■■ – ($p<0.01$); ■■■ – ($p<0.001$); Δ – of the AHP and index groups: Δ – ($p<0.05$); ΔΔ – ($p<0.01$); ΔΔΔ – ($p<0.001$); ° – of the AHP and experimental groups: ° – ($p<0.05$); °° – ($p<0.01$); °°° – ($p<0.001$).

According to the data analysis of Table 2, administration of intensive supportive therapy in six months has proved that the concentration of NO metabolites in the blood has increased in 1.3 times up to the level of (10.35 ± 1.89) $\mu\text{mol/l}$ ($t=1.00$; $p>0.1$), while in patients of the index group, the average values of the content of NO metabolites in the serum have hardly reached (8.95 ± 1.26) $\mu\text{mol/l}$. Thus, the use of roflumilast and quercetin in the complex therapy has a stimulating effect on the synthesis of NO in patients with COPD of the 3rd severity level in an exacerbation phase accompanied with SCAD SEA of the 1st – 2nd FC and is an effective combination of drugs for the recovery of its metabolism.

Conclusion

The combination of roflumilast and quercetin in the complex therapy for patients with severe COPD in an exacerbation phase accompanied by SCAD SEA of the 1st – 2nd FC improves endothelial function, restores the structure of peripheral vessels and promotes the normalization of NO synthesis. At the same time, clinical potential of the complex therapy for patients with COPD in an exacerbation phase combined with SCAD requires further study within the framework of specially planned clinical trials as well as in routine clinical practice.

Prospects for further research are as follows: there are good reasons to study the effects of this drug combination on the inflammatory marker profile, endothelial function of peripheral and coronary arteries in patients with COPD in an exacerbation phase accompanied by SCAD.

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Реферати
**ПАТОГЕНЕТИЧНІ ЕФЕКТИ В ЛІКУВАННІ
ПОСДНАНОЇ КАРДІО-РЕСПІРАТОРНОЇ
ПАТОЛОГІЇ**
**Яцишин Р.І., Герич П.Р., Дидушко О.М.,
Шаповал О.А.**

Вивчення можливості медикаментозної корекції ендотеліальної дисфункції (ЕД), структурних змін периферичних артерій та синтезу кінцевих продуктів метаболізму оксиду азоту шляхом застосування комбінації рофлуміласту і кверцетину у складі базової терапії. На відміну від базової, застосування комплексної терапії супроводжувалося через 6 місяців вірогідним збільшенням початкової швидкості на 18,76 % від $(0,61 \pm 0,04)$ м/с до $(0,75 \pm 0,04)$ м/с ($t=2,47$; $p<0,05$) та вірогідним зменшенням вихідного діаметру плечової артерії до $(3,74 \pm 0,28)$ мм ($t=2,49$; $p<0,05$). Призначення комплексної терапії через 6 місяців засвідчило зростання концентрації в крові метаболітів ОА в 1,3 раза до $(10,35 \pm 1,89)$ мкмоль/л ($t=1,00$; $p>0,1$) при нормі $(12,05 \pm 2,11)$ мкмоль/л. Застосування комплексної терапії у хворих на хронічне обструктивне захворювання легень (ХОЗЛ) важкого ступеня у фазі загострення за посидання зі стабільною ішемічною хворобою серця стабільна стенокардія напруги (СІХС ССН) I-II ФК сприяє відновленню ендотеліальної функції, поліпшує структурні зміни периферичних артерій і має стимулюючий ефект на синтез ОА.

Ключові слова: стабільна ішемічна хвороба серця, хронічне обструктивне захворювання легень, ендотеліальна дисфункція, оксидантний стрес.

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**ПАТОГЕНЕТИЧЕСКИЕ ЭФФЕКТЫ В ЛЕЧЕНИИ
СОЧЕТАННОЙ КАРДИО-РЕСПИРАТОРНОЙ
ПАТОЛОГИИ**
**Яцишин Р.И., Герич П.Р., Дидушко О.Н.,
Шаповал О.А.**

Изучение возможности медикаментозной коррекции эндотелиальной дисфункции, структурных изменений периферических артерий и синтеза конечных продуктов метаболизма оксида азота путем применения комбинации рофлумиласта и кверцетина в составе базовой терапии. В отличие от базовой, применение комплексной терапии сопровождалось через 6 месяцев вероятным увеличением начальной скорости на 18,76% от $(0,61 \pm 0,04)$ м / с до $(0,75 \pm 0,04)$ м / с ($t = 2,47$; $p < 0,05$) и возможным уменьшением исходного диаметра плечевой артерии до $(3,74 \pm 0,28)$ мм ($t = 2,49$; $p < 0,05$). Назначение комплексной терапии через 6 месяцев показало рост концентрации в крови метаболитов оксида азота в 1,3 раза до $(10,35 \pm 1,89)$ мкмоль / л ($t = 1,00$; $p > 0,1$) при норме $(12,05 \pm 2,11)$ мкмоль / л. применение комплексной терапии у больных на хроническую обструктивную болезнь легких тяжелой степени в фазе обострения при сочетании со стабильной ишемической болезнью сердца, стабильная стенокардия напряжения I-II ФК способствует восстановлению эндотелиальной функции, улучшает структурные изменения периферических артерий и имеет стимулирующий эффект на синтез оксид азота.

Ключевые слова: стабильная ишемическая болезнь сердца, хронические обструктивные заболевания легких, эндотелиальная дисфункция, оксидантный стресс.

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