Original article:

Effect of low-intensity laser radiation on hemostasis in patients with chronic obstructive pulmonary disease

Natalya M. Balabina[1], Alexey N. Kalyagin[2], Tatyana M.Maksikova[3], Vadim A. Dulskiy[4], Valentina A. Haptanova[5], Olga V. Zhigalova[6], Larisa S. Andreeva[7]*

Abstract:

Objective. The study presents results of the low-intensity intravenous (IV) laser radiation effect on some indicators of the hemostasis system and respiratory function of 83 patients with a chronic lung disease (COPD), stable phase, II-III (after GOLD scale), including 51 men and 32 women. The average COPD duration was 9.6±4.4 years. ***Materials and methods***. All patients with COPD were randomly divided into 2 groups - comparison (30 people) and main (53 people). The control group consisted of 20 practically healthy people, matched by sex and age. Patients in the control group received only standard drug therapy with IGCC/DBA combination (budesonide/formoterol, salmeterol/fluticasone propionate inhalation at a therapeutic dose corresponding to the COPD clinical symptoms severity). ***Result and Discussion***. In addition to the basic treatment, the main group received a course of intravenous low-intensity laser radiation. As established before the treatment initiation, patients with COPD experienced a decrease in FEV_1, Tiffno index, SaO2. ***Conclusion***. The respiratory function disruption was accompanied by a significant activation of plasma hemostasis (prothrombin time shortening, thrombin time, activated partial thromboplastin time) and a significant increase in platelet aggregation (increase in the aggregation degree, aggregation rate, decrease in the aggregation time). At the same time, in patients with COPD, a significant decrease in anticoagulant activity was observed before treatment, particularly antithrombin III decrease when compared with the control group ($p < 0.05$) and CRP (main group: 0.86±0.02; control group: 0.85±0.02). The introduction of low-intensity laser radiation into the patients complex with COPD led to the these parameters normalization.

Keywords: COPD, plasma hemostasis, platelet aggregation, low-intensity intravenous laser radiation

Bangladesh Journal of Medical Science Vol. 18 No. 03 July'19. Page : 586-592
DOI: https://doi.org/10.3329/bjms.v18i3.41633

Introduction

Chronic obstructive pulmonary disease (COPD) is referred as a serious medical and socio-economic issue due to its high prevalence, progressive increase in irreversible obstruction, aggravated by comorbid background, early disability of the active working age population and high mortality[1,2]. Chronic pollutant-induced inflammation leads to the gross morphological changes development in all lung structures with the cardiovascular system, respiratory muscles involvement, extrapulmonary systemic inflammatory process manifestations[3-5]. At present, studies has proven that the inflammation, fibrosis and exudate in the small bronchi lumen occuring in COPD correlates with the FEV_1 degree decrease and the FEV_1/FVC ratio. Peripheral airway obstruction blocks lung airflow in the expiratory phase (so-called "air traps"), and as a result the hyperinflation develops. The state is accompanied by inspiratory volume decrease, more pronounced while exercise.

1. Natalya M. Balabina, Irkutsk State Medical University, Irkutsk, Russia
2. Alexey N. Kalyagin,
3. Tatyana M.Maksikova,
4. Vadim A. Dulskiy,
5. Valentina A. Haptanova,
6. Olga V. Zhigalova,
7. Larisa S. Andreeva,
   Irkutsk state medical University, Irkutsk, Russia

Correspondence to: Natalya M. Balabina, Irkutsk State Medical University, Irkutsk, KrasnogoVosstaniya 1, 664003, Russia; +79148998978; Email : bnalya@yandex.ru

As a the increasing hyperinflation result, the COPD patient experience shortness of breath, which gradually leads to a decrease in exercise tolerance[2,5]. As a response to ongoing recurrent and increasing hypoxia total microcirculatory disorders develop in the vital organs and tissues of COPD patients. COPD-related recurrent hypoxia and hypercapnia episodes, increased intrathoracic pressure due to airway obstruction, oxidative stress, systemic inflammation can directly lead to the formation or aggravation of existing endothelial dysfunction[6-8]. Despite the continuous improvement in the basic treatment approach towards such patients with GOLD program, the COPD patients number with progressive respiratory failure as well as multiorgan lesions increases every year, which is accompanied by the severe complications risk and requires the search for new treatment methods[5].

Meanwhile, the study of plasma hemostasis and platelet aggregation involvement in the systemic inflammation in COPD could affect the new treatment methods introduction for these patients, and thus improve the this serious disease course. Until now, COPD baseline therapy is determined by the symptoms severity, complications frequency and the disease effect on the patient according to CAT scale[9] and does not consider changes in plasma hemostasis and platelet aggregation. It includes dual therapy with prolonged bronchodilators, eliminating the “air trap” symptom.

In case of repeated disease exacerbations (>2 or more than one with hospitalization), antibiotics and inhalation glucocorticosteroids are actively added to the COPD treatment patients[10]. However, all these medicines have many side effects and do not always lead to the complete COPD symptom disappearance, such as shortness of breath. Thus, M-cholinolytics cause a mucociliary clearance violation, and glucocorticoids and antimicrobial drugs cause cellular and humoral immunity inhibition. Moreover, the frequent antibiotics use for COPD exacerbations causes colonization of the respiratory tract mucous membranes with gram-negative microorganisms[7,11]. Numerous literature data indicate the laser radiation use in complex therapy of numerous systemic inflammatory diseases.

Therefore, considering COPD as a systemic inflammatory disease and deciphering plasma hemostasis and platelet aggregation changes during the COPD stable phase may lead to the introduction of new treatments into the complex COPD therapy, including low-intensity intravenous laser blood radiation. However, data of low-intensity laser radiation use for the chronic obstructive pulmonary disease treatment are virtually absent.

Problem Statement

The the medico-social aspect relevance of the COPD problem requires the analysis and study of all the pathogenesis parts of systemic inflammation in COPD. Systemic COPD effects on the body include the formation of the inflammatory process, the participants and markers of which are C-reactive protein (CRP) and fibrinogen[3,12-14]. Systemic inflammatory response is impossible without the intravascular neutrophils and hemostasis system involvement. Some authors consider an increase in plasma fibrinogen concentration as one of the key factors to consider COPD patients prognosis stratification[15,16]. High fibrinogen levels in the patients blood can change conditions hemostasis at all levels significantly, and create prerequisites for COPD thrombotic complications[15,17,18]. COPD is characterized by neutrophils and T-lymphocytes accumulation in the pulmonary parenchyma and the respiratory tract wall[17,18]. The intercellular interactions of neutrophils and T-lymphocytes and their functional state are regulated by cytokines and immunoglobulins[12,19]. Inflammation modulators infiltration (IL-6, α-TNF, IL-1β, IL-12) into the systemic circulation of patients with COPD stimulates hepatocytes to synthesize acute-phase proteins, C-reactive protein (CRP), fibrinogen[17,18]. Under the systemic and tissue hypoxia influence, the antithrombogenic endothelium activity the (thromboxane hyperproduction, reduced prostacyclin)[20] and the blood rheology may change[21]. So far, it is known that rheological disorders in patients with COPD are associated with intravascular RBC aggregation and local stasis in microvessels. The indicators participation of plasma hemostasis and platelet aggregation in this process in COPD patients is still not known and requires further study.

Objective: Study the low-intensity laser radiation effect on some indicators of hemostasis system and respiratory function in patients with COPD.

To achieve this objective, the following tasks were defined as follows:

1. Study the PLC aggregation properties dynamics

in patients with COPD under the intravenous low-intensity blood laser radiation influence;
2. Investigate some hemostasis indicators dynamics (activated partial thromboplastin time, prothrombin time, thrombin time, antithrombin III, activity of the protein C system, von Willebrand factor) under the influence of low-intensity laser radiation in patients with COPD;
3. Evaluate the low-intensity laser radiation effect on the indicators dynamics of respiratory function in patients with COPD and the possibility of its use in the these patients complex treatment.

Research Methods

To achieve this goal and objectives, we examined 83 patients with COPD, including 51 men and 32 women. The average COPD duration was 9.6±4.4 years. COPD diagnosis, including an its severity assessment, was carried out on the generally accepted criteria basis [2]. Patients who participated in the study had moderate to severe COPD stage (according to GOLD). All patients with COPD were randomly divided into 2 groups - control (30 people) and main (53 people). The comparison group included 20 healthy people, comparable by sex and age, who were examined to obtain average normal values of the studied parameters. Age median (Me) in the main group was 70 (61; 74) years; Age Me in the control group was 70 years (61; 78); in the comparison group - 70 (60; 73) years. All patients were examined during the COPD stable stage. Clinical and laboratory examination of all patients during the study was carried out according to a single scheme before the laser therapy initiation and 5-7 days after the course end. The examination included: anamnesis, blood pressure measurement, clinical and biochemical blood tests, urinalysis, determination of activated partial thromboplastin time, prothrombin time, thrombin time, activity of the protein C system, antithrombin III, von Willebrand factor, chest X-ray, ECG in 12 standard leads, echocardiography, internal organs ultrasound. Respiratory function assessment was carried out using a standard SpiroUSB method using Spida5 software (Micro Medical Limited, Rochester, UK) in accordance with the recommendations of the American Thoracic and European Respiratory Communities[22]. Platelet aggregation properties and von Willebrand factor activity study was performed using the SOLAR AP 2110 platelet aggregation analyzer. The plasma coagulation properties study was performed using standard reagents from NPO Renam on a CGL 2110 coagulometer from SOLAR (Belarus).

The exclusion criteria were as follows: bronchial asthma, atopy, allergic rhinitis, tuberculosis, acute infectious diseases, chronic liver and kidney diseases, coagulation disorders, systemicglucocorticosteroids intake for 2 months prior to the study, inability to properly perform a respiratory maneuver when testing respiratory function (RF). Patients included in the study gave informed consent for participation in it.

Patients in the control group received only standard medication therapy using IHCS/DBA combination (budesonide/formoterol, salmeterol/ fluticasone propionate inhalation at a therapeutic dose corresponding to the clinical COPD symptoms severity). In addition to the basic treatment, the main group received a intravenous low-intensity laser radiation course.

The intravenous low-intensity laser radiation course was conducted using the “Matrix-VLOK” apparatus (“Matrix”, Russia). The use of a KL-VLOK radiating head (wavelength: 635 nm, disposable fiber output power: 1.5-2.0 mW; 15 minutes) and a KL-VLOK-365 laser head (for UFOC, wavelength: 365 nm) alternated every other day within 5 minutes. Procedures were performed daily for 10 days without holidays.

The research results were processed using the STATISTICA 7.0 software package. Statistical data processing was carried out according to generally accepted criteria of variational-statistical analysis with the average values calculation (M), arithmetic average error (m). To assess the mean differences statistical significance in the cases of two samples, t-test was used (Student’s t-test). Differences were considered as significant with an error probability $p < 0.05$.

Ethical approval: This research protocol was approved by the Ethics Committee of Irkutsk State Medical University, Irkutsk, Russia.

Results

While comparing the initial clinical instrumental parameters of the studied groups, in one case there were no statistically significant differences ($p > 0.05$). Most patients had a reduced level of blood oxygen saturation. The BR in patients from both groups was 23.54±1.29 and 22.90±1.34 beats/min respectively. In both groups were noted with sinus tachycardia, in the main group the heart rate was 98.63±7.74, in the control group - 99.14±7.81 beats/min (table 1).

Table 1.Patients characteristics with COPD

Indicator	Main group of patients with COPD (n=53)	Control group of patients with COPD (n=30)
Age, years	Me:70(61;74)	Me:70(61;78)
Male/female	32/21	19/11
Smokingindex, packs/year	22.2±1.3	21.6±1.4
COPD duration, years	9.9±3.4	10.2±4.8
COPD stage after GOLD n, II/III	31/22	21/9
FVC, %	67.76±1.83	68.44±1.71
FEV_1, %	41.97 ±1.92	41.12 ±1.43
FEV_1/FVC	48.1±1.6	47.9±1.64
BR/min	23.54±1.29	22.90±1.34
HR/min	98.63±7.74	99.14±7.81
SaO_2, %	92.74±0.71	92.28±0.91

In the study of changes in the plasma hemostasis, within the patients with COPD of the main and control groups, significant signs of hypercoagulation were revealed before treatment: prothrombin time, thrombin time, activated partial thromboplastin time shortening (tab.2). At the same time, a significant decrease in anticoagulant activity was observed in patients with COPD before treatment, as evidenced with a decrease in antithrombin III value as compared with the healthy group ($p < 0.05$) and protein C (main group: 0.86±0.02; control group: 0.85±0.02).

Table 2. Plasma hemostasis in patients with COPD before treatment

Indicator	Main COPD group before treatment	Control COPD group before treatment	Healthy group	P_1	P_2
APPT, sec	21.2±0.5	21.5±1.2	31.9±1.9	<0,01	>0,05
PTT, sec	12.1±1.7	12.2±1.3	21.0±0.6	<0,01	>0,05
TT, sec	11.0±0.9	11.3±0.2	16.1±0.7	<0,01	>0,05
AT III,%	84.8±1.1	86.5±1.4	100±6.3	<0,05	>0,05
Protein C, (Hemeoxygenase)	0.86±0.02	0.85±0.02	1.05±0.06	<0,001	>0,05
P_1- differences significance between main, control and healthy groups; P_2 – differences significance between main and control COPD group;					

After treatment (table 3), there was a significant increase in the APTT in the main group of patients with COPD from 21.2±0.5 to 29.4±0.5 sec ($p<0.01$), PTV from 12.1±1.7 to 19.1±0.2 ($p<0.05$). In the control group, there is also a tendency to an increase for these indicators: APTT (from 21.5±1.2 to 23.8±1.1; $p>0.05$), PTT (from 12.2±1.3 to 15.9±0.2; $p>0.05$). However, the increase in these indicators cannot be considered as reliable.

Table 3. Plasma hemostasis dynamics in patients with COPD after treatment

Indicator	Main COPD group before treatment	Control COPD group before treatment	Healthy group	P_1	P_2	P_3
APPT, sec	29.4±0.5	23.8±1.1	31.9±1.9	0,05	<0,01	<0,01
PTT, sec	19.1±0.2	15.9±0.2	21.0±0.6	0,05	<0,05	<0,05
TT, sec	16.7±0.1	14.4±1.1	16.1±0.7	0,06	<0,05	<0,01
AT III,%	100.3±0.8	96.6±3.3	100±6.3	>0,05	>0,05	>0,05
Protein C, (Hemeoxygenase)	0.98±0.03	0.89±0.04	1.05±0.06	<0,05	<0,01	<0,01

P_1- differences significance between main and healthy COPD group;
P_2–differences significance between control and healthy COPD group;
P_3–differences significance between main and control COPD group

After treatment, both in the main and control groups, an antithrombin III level increase was observed, while this indicator dynamics in the main group was significant ($p<0.05$). In the control group, there was no significant difference between the antithrombin III level before and after treatment ($p>0.05$). In the main group of patients, the main physiological anticoagulant protein C activity increased significantly after treatment from 0.86±0.02 to 0.98±0.03 ($p<0.01$), while in the control group no significant increase in protein C was observed.

In the platelet aggregation study, a significant increase was noted in both groups (table 4-5).

Table 4. Platelet aggregation dynamics in the main group with COPD before and after treatment

Indicator	Main group		Healthy group	P_1	P_2
	Before treatment	After treatment			
Aggregation degree, %	87.7±2.8	61.8±1.9	60.2±1.3	<0,001	<0,001
Aggregation speed, %/min	48.6±4.4	18.1±1.7	19.2±1.3	<0,001	<0,001
Aggregationtime, min	6.4±0.3	8.1±1.2	8.6±1.2	>0,05	>0,05

P_1 - differences significance between main and healthy COPD group;
P_2-differences significance between main group before and after treatment;

No significant differences in the aggregation activation degree between the indicators of the main and control groups were noted. Thus, the main and control groups with COPD before treatment showed a significant increase in the degree and aggregation rate. Aggregation degree in the main group was 87.7±2.8% ($p<0.001$), in the control group - 86.4±3.4% ($p<0.001$). The increase in the aggregation rate in the main group was 48.6±4.4%/min ($p<0.001$), in the control group - 46.2±1.9% min (($p<0.001$).

Table 5. Dynamics of platelet aggregation ability in control group with COPD before and after treatment

Indicator	Controlgroup		Healthy group	P_1	P_2
	Before treatment	After treatment			
Aggregation degree, %	86.4±3.4	75.6±2.1	60.2±1.3	<0,001	>0,05
Aggregations peed, %/min	46.2±1.9	28.9±1.5	19.2±1.3	<0,001	<0,051
Aggregationtime, min	6.2±0.3	6.4±0.5	8.6±1.2	>0,05	>0,05

P_1 - differences significance between main and healthy COPD group;
P_2 -differences significance between main group before and after treatment;

After treatment, the aggregation indicators normalized only for the main group with COPD.

The study of respiratory function dynamics indicators, heart rate, respiratory movements per minute and oxygen saturation index allowed us to establish a significant change in these indicators before treatment in both groups (table 6).

After complex treatment with the introduction of IV low-intensity laser radiation in the main group with COPD, these indicators have significantly improved. Thus, pulmonary exhale function improved, as evidenced by a significant increase in the forced vital capacity (FVC) from 67.76±1.83% to 74.3±1.92% ($p<0.05$). Such indicators as forced expiratory volume in 1 second have significantly increased (from 41.97±1.92% to 59.8±2.12%; $p<0.01$), Tiffno index (from 48.1±1.6 to 61.2±1.31; ($p<0.01$) oxygen saturation (from 92.74±0.71 to 95.6±0.62%; $p<0.05$). BR and HR per minute decreased significantly. In the control group with COPD, FEV_1, decrease in BR and HR per minute was less pronounced ($p <0.05$). FVC indices, index Tiffno, SaO_2 didn't change significantly.

Table 6. RF and HR dynamics under the treatment influence in the main and control groups

Indicator	Main group		Control group		P_1	P_2
	Before treatment	After treatment	Before treatment	After treatment		
FVC, %	67.76±1.83	74.3±1.92	68.44±1.71	71.3±1.94	<0,05	>0,05
FEV_1, %	41.97 ±1.92	59.8±2.12	41.12 ±1.43	51.1±2.02	<0,01	<0,05
FEV_1/FVC	48.1±1.6	61.2±1.31	47.9±1.64	52.4±1.21	<0,01	>0,05
HR/min	23.54±1.29	18.13±0.92	22.90±1.34	20.17±0.82	<0,05	<0,05
HR/min	98.63±7.74	82.41±1.23	99.14±7.81	89.11±1.13	<0,01	<0,05
SaO_2, %	92.74±0.71	95.6±0.62	92.28±0.91	93.6±0.57	<0,05	>0,05

P_1 -differences significance of main group before and after treatment
P_2 - differences significance of control group before and after treatment

Thus, the respiratory function indicators positive dynamics, respiratory movements frequency per minute, heart rate frequency per minute and oxygen saturation in a group of patients who received complex therapy with the intravenous low-frequency laser therapy inclusion were established.

Conclusion

Our results suggest, that patients with COPD show significant changes in respiratory function, plasma hemostasis activation (shortening the prothrombin time, thrombin time, activated partial thromboplastin time) prior to treatment with the antithrombin III level decrease. Also data indicates, that even in the stable COPD phase before the treatment start, all patients experience hypercoagulation, which is significantly reduced in the group of patients who received treatment with the IV low-intensity laser radiation inclusion.

As a result of the platelet aggregation activity study in patients with COPD, an increased aggregation activity was noted in both groups, as evidenced by a significant increase in the aggregation degree and rate. After treatment, there was a reliable normalization of all studied parameters only in the main group, whereas in the control group none of the studied parameters reached the normal value.

RF and HR indicators dynamics analysis under the treatment influence showed that a significantly more pronounced increase in indicators of forced expiratory volume in the first second, Tiffno index, respiratory movements per minute, heart rate per minute and oxygen saturation was achieved in the main group compared with the control group.

Based on the study results, it can be concluded that the inclusion of intravenous low-intensity laser radiation in the complex therapy for patients with COPD contributes to the plasma hemostasis, aggregation ability, spirometry, oxygen saturation normalization and shortness of breath reduction.

Thus, the intravenous low-intensity laser radiation in the complex therapy of chronic obstructive pulmonary disease is accompanied by the plasma hemostasis and platelet aggregation properties normalization. The intravenous low-intensity laser radiation inclusion in the complex therapy of COPD is pathogenetically substantiated, since it helps to eliminate hypercoagulation and platelet hyperaggregation, a decrease in respiratory failure as

a result of a decrease in airway obstruction and an increase in oxygen saturation.

Conflict of interest: Nil

Author's contribution:

Idea owner of this study: Natalya M. Balabina, Alexey N. Kalyagin, Tatyana M. Maksikova, Vadim A. Dulskiy,

Study design: Natalya M. Balabina, Alexey N. Kalyagin, Tatyana M.Maksikova, Vadim A. Dulskiy

Data gathering: Natalya M. Balabina, Valentina A. Haptanova, Olga V. Zhigalova, Larisa S. Andreeva

Writing and submitting manuscript: Natalya M. Balabina, Alexey N. Kalyagin, Tatyana M. Maksikova, Vadim A. Dulskiy.

Editing and approval of final draft: All authors

References:

1. Vertkin AL, Rumyantsev MA, Skotnikov AS. Comorbidity. *Clinical medicine* 2012; **10**: 4–11.
2. Chuchalin AG, Avdeev SN, Aysanov ZR, Belevskiy AS, Leshchenko IV, Meshcheryakova NN, ... Shmelev EI. Russian respiratory society. Federal guidelines on diagnosis and treatment of chronic obstructive pulmonary disease. *Russian Pulmonology* 2014;**(3):** 15-54.
3. Balabina NM. The prevalence of iron deficiency anemia in patients with chronic obstructive pulmonary disease and its effect on the course of the disease. *Innovative technologies in pharmacy: Collected scientific papers. Irkutsk State Medical University, Irkutsk*2018;**5**: 301-304..
4. Dvoretsky LI. Anemia in patients with chronic obstructive pulmonary disease: is it co-morbidity or a systemic manifestation? *Pulmonology* 2012;**2**: 5–11.
5. Chuchalin AG. *Pulmonology*. Moscow, GEOTAR-Media, 2016.
6. Anzueto A. Impact of exacerbations on COPD. *EurRespir Rev.* 2010; **19** (116): 113—118.
7. Simoens S, Laekeman G, Decramer M. Preventing COPD exacerbations with macrolides: a review and budget impact analysis. *Respir Med.* 2013;**107** (5): 637—648.
8. Tompkins DH, Besnard V, Lange AW, Keiser AR, Wert SE, Bruno MD, Whitsett JA. Sox2 Activates Cell Proliferation and Differentiation in Respiratory Epithelium. *Am J Respir Cell Mol Biol.* 2011;**45**: 101–110.
9. Barabanova EN. GOLD 2017: what change were made in global strategy of treatment of chronic obstructive pulmonary disease and why? *Pulmonology* 2017; **27**(2): 274-282.
10. Zyryanov SK, Frolov MY, Belevskiy AS. Clinical efficacy and cost-effectiveness of therapy for chronic obstructive pulmonary disease. *Practical pulmonology* 2016; **4**: 76-84.
11. Mashkovsky MD. *Medicines*. Moscow, Novaya volna, 2010.
12. Barnes PJ. The cytokine network in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2009; **41**(6): 631—638.
13. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *Jama* 2013; **309**(22): 2353-2361.15
14. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, ... Meade TW. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thrombosis and haemostasis* 2000; **84**(08): 210-215.
15. Polunina OS, Mikhailova IA, Kudryasheva IA. The state of the hemostatic system in patients with chronic obstructive pulmonary disease in the elderly. *Fundamental research* 2005; **2**: 75.
16. Valvi D, Mannino DM, Müellerova H, Tal-Singer R. Fibrinogen, chronic obstructive pulmonary disease (COPD) and outcomes in two United States cohorts. *International Journal of Chronic Obstructive Pulmonary Disease*2012;**7**: 173–182.
17. KadushkinAG,Taganovich AD, KartunLV. Plasma cytokine levels in non-smoking and smoking patients with chronic obstructive pulmonary disease. *Pulmonology* 2013; **6**: 27—32.
18. Kadushkin AG, Shman TV, Novikov VP. Quantitative change of regulatory T-lymphocytes in patients with chronic obstructive pulmonary disease. *Pulmonology* 2013;**3**: 26—30.
19. Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlösser NJ, Wouters EF, COSMIC Study Group. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest*2008;**133**: 350–357.
20. Malyavin AG, Epifanov BA, Glazkova II. *Rehabilitation for respiratory diseases*. Moscow, GEOTAR-Media, 2010.
21. AkhmetzyanovaEKh, Gainitdinova VV, Sharafutdinova LA.*Management of patients with chronic heart failure with intact systolic function and te background of severe COPD in the exacerbation phase of breast cancer №2*, 2014. https://www.rmj.ru/articles/kardiologiya/Vedenie_pacientov_s_hronicheskoy_serdechnoy_nedostatochnostyyu_s_sohrannoy_sistolicheskoy_funkciey_na_fone_tyaghelogo_techeniya_HOBL_v_faze_obostreniya/
22. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, ... Gustafsson P. Standardisation of the measurement of lung volumes. *European respiratory journal* 2005; **26**(3): 511-522.