ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Ways To Improve The Effects Of Pulmonary Rehabilitation In Patients With Chronic Obstructive Pulmonary Disease.

Luev IA, Tokmachev RE*, Ovsyannikov ES, Shkatova YS, and Chernik TA.

Voronezh State Medical University, 10 Studencheskaya Street, Voronezh, Russia 394036.

ABSTRACT

The literature review deals with the epidemiology, mechanisms of development, peculiarities of diagnostics and treatment of comorbid chronic heart failure and chronic obstructive pulmonary disease. It is shown that comorbidity of chronic heart failure and chronic obstructive pulmonary disease significantly worsens the prognosis in this category of patients. Activation of the pro-inflammatory mediators such as tumor necrosis factor (TNF), interleukins (IL) 1, 6, 8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and active forms of oxygen and proteases (elastase, matrix metalloproteinases 9 and 12) plays an important role in the pathogenesis of both illnesses. Differential diagnosis in chronic heart failure and chronic obstructive pulmonary disease patients is somewhat difficult as both illnesses can be presented by similar clinical symptoms. Medical treatment of comorbid chronic heart failure and chronic obstructive pulmonary disease still stays quite a challenge for an attending physician and requires a special approach to every individual.

Keywords: chronic heart failure, chronic obstructive pulmonary disease, comorbidity, natriuretic peptides, pro-inflammatory mediators.

Corresponding author

Pulmonary rehabilitation of patients with respiratory diseases is one of the important tasks in modern healthcare. Every year in Russia, at least 10 million people need comprehensive rehabilitation of the bronchopulmonary system, and in recent years there has been a tendency to steady growth, especially in patients with chronic obstructive pulmonary disease [6, 7]. For a long time, rehabilitation measures were understood as sanatorium-resort treatment, as a result of which their importance at the outpatient stage was underestimated [7].

According to the latest joint recommendations of the American Thoracic Society and the European Respiratory Society, pulmonary rehabilitation is a system of measures for a patient with a chronic respiratory disease that has a clinically relevant course of the disease and a violation of the level of daily activity. Integrated into daily treatment, pulmonary rehabilitation is designed to reduce the manifestations of the disease, optimize functional status, improve cooperativeness and reduce the cost of treatment by stabilizing or reducing the systemic manifestations of the disease. Pulmonary rehabilitation of patients with respiratory diseases is one of the important tasks in modern healthcare.

The factors causing a decrease in exercise tolerance in patients with COPD include ventilation disorders due to the development of an air trap and hyperinflation, which causes shortness of breath during physical load of varying severity depending on the stage of the disease. It should also be noted the increased requirements for additional ventilation in patients with COPD due to general detraining and dysfunction of the peripheral muscles. The second important factor is the changes in respiration. By itself, hypoxia causes a violation of exercise tolerance.

In addition, increasing the concentration of lactic acid in the muscles led to the accumulation of CO2. Dysfunction of skeletal muscles is characterized by the development of changes in peripheral muscles, consisting in loss of muscle mass, weakness of muscles, leading to a decrease in exercise tolerance, which is a manifestation of the systemic effects of the disease, hypodynamia and sometimes taking systemic steroids are well described.

Disorders of the respiratory muscles - the reduction of their contraction increases with the progression of the disease, and most recently significant changes occur in the diaphragm. This leads to an increased feeling of shortness of breath and a further reduction in exercise tolerance [1].

Changes in the heart. The pathology of the cardiovascular system is caused by various ways, the most significant of which is an increase in afterload of the right ventricle as a result of an increase in resistance in the pulmonary artery system, which in turn leads to right ventricular hypertrophy with the possible development of right ventricular failure. To this are added the violation of the left ventricle due to the displacement of the interventricular septum, the increase in pressure in the pulmonary artery during exercise, as well as myocardial detraining as a result of hypodynamia [2].

Thus, as can be seen from the above, one of the important tasks in the development of a pulmonary rehabilitation system is the training of the respiratory muscles. In pulmonary rehabilitation, physical training considered as the main event to improve physical abilities. This aspect is the most studied for patients with COPD. In addition to directly improving the function of peripheral muscles, physical training helps to improve motivation, improve mood, reduce symptoms of the disease and have a positive effect on the cardiovascular system. Along with general physical workouts, the training of respiratory muscles using various instruments and devices is of considerable interest. The effectiveness of training respiratory muscles remains the subject of intensive study [3-5]. The high efficiency of the increasing inhalation and expiratory threshold loads is shown, which leads to an improvement in exercise tolerance and an improvement in the functional state of the lungs. A recent meta-analysis showed that the use of only training of the respiratory muscles in patients with moderate to severe COPD led to a significant reduction in the severity of shortness of breath. The joint use of general physical training and training of the respiratory muscles leads to an additional increase in the strength and endurance of the respiratory muscles. Respiratory trainers are used for training respiratory muscles. These are the so-called PEP and PIP simulators. The PEP simulator creates resistance on exhalation, and PIP– on inspiration, so the patient is forced to make an effort, and the muscles involved in the act of breathing on inspiration and exhalation are activated. During the usage of simulators that create resistance to inhalation, the patient is forced to make an effort when inhaling, thereby increasing the inhalation time and respiration rate decreases, with an increase in the volume of inhaled air. The most famous in Russia simulator of this type is the Frolov simulator.

Specially designed instruments are used as expiratory simulators (PEP), with or without adjustable resistance level. There are no domestic analogues with a similar set of functions and a range of tasks to be solved, and the Frolov simulator and his ilk work in a very limited range of loads, which absolutely does not allow to use them for these purposes effectively, safely, and most importantly in a wide contingent of patients with different severity. This is especially true for patients with COPD of severe and very severe course, as well as with obesity or underweight, because they have initially low Pimax values (the maximum possible inspiratory or expiratory effort for this patient at the given moment). Foreign counterparts of the obviously unjustifiably expensive, in fact, represent the same Frolov simulator, only in a modern digitized shell. Taking into account the best components of the respiratory muscle training method developed on the basis of many years of research, namely the training program with the definition of the so-called Pimax and further gradual increase of loads with a certain interval in percent of this value. The computer system developed by us allows this process to be carried out as smoothly as possible and flexibly without sudden drops and pronounced thresholds, adapting automatically to a specific patient using biofeedback, creating comfortable, safe and effective individualized training regimes that best suit the severity of the disease, the capabilities of the patient. There is an opportunity to train the respiratory muscles of both inspiratory and expiratory types, and at the same time within the same training session.

Training effectiveness can be monitored not only by the growing strength of the respiratory muscles, but more importantly for practical health care, by assessing the increase in spirometric parameters, which is achieved using an integrated pneumotachometric sensor and software features [6]. This allows real-time judging of the prognostically significant success of workouts in a more understandable context for the practical physician, extrapolating these data to the severity of the disease, assessed with using the usual and recommended worldwide spirometry parameters.

Many sources indicate the need for uniformity in the ultimate goals of ongoing pulmonary rehabilitation, such as dyspnea reduction, relief of clinical symptoms of the disease, prevention of exacerbations, improvement of exercise tolerance, improvement of the overall quality of life [8].

It is worth noting that the need to quit smoking is highlighted as one of the main factors for successful pulmonary rehabilitation. It is recommended to exclude exposure to tobacco smoke in the early stages of chronic obstructive pulmonary disease. This is explained by the fact that the functional state of the patient and the adaptive capabilities of the body make it possible to use mainly physical rehabilitation methods [11,14].

Rehabilitation activities are mainly carried out outside the period of exacerbation of the disease with the clinical stability of the patient.

In most sources there is no clear definition of the place of pulmonary rehabilitation in complex methods of treatment of patients with COPD.

In modern clinical standards, recommendations, respiratory rehabilitation is considered in one of the subsections of treatment for stable COPD and the optimal time for its beginning remains unclear [1,2,8-10].

The disadvantages of pulmonary rehabilitation include the limited duration of the results achieved. Currently, there are works confirming the possibility of maintaining the resulting improvement from 1 to 2 years, the tendency to a gradual decrease in exercise tolerance over time is obvious. Some studies reported that the effect of pulmonary rehabilitation gradually decreases to baseline after 6–12 months, but after 1 year it remains higher than in control groups. Improved quality of life is more consistently maintained than exercise tolerance, sometimes for 2 years after rehabilitation.

The question of the best means of maintaining the results of PR remains. Great importance for maintaining the results of pulmonary rehabilitation is attached to such factors as motivation, family and/or social support, living conditions and a stable course of the disease. In patients with a clinically stable course of COPD, who continue to conduct physical rehabilitation at home after the main course, it is more likely that the achieved level of physical tolerance will be maintained for a long period of time.

Many researchers believe that the most suitable place for carrying out pulmonary rehabilitation is a hospital, outpatient clinic is second in importance, and carrying out pulmonary rehabilitation at home is

considered as a necessary step when it is impossible to carry out pulmonary rehabilitation in inpatient and outpatient settings. At the same time, the standards-recommendations note that both the inpatient, and outpatient, and home stages are equally successful. Patients with COPD, who were trained in the principles of self- maintenance, were less likely to need hospitalization, less often visited emergency departments and had fewer unplanned visits to the doctor. In one study, the course of 18-week community-acquired pulmonary rehabilitation resulted in a decrease in the total cost of the average annual cost of $ 344 per patient. Pulmonary rehabilitation in a hospital may consist of planned programs, and the patient is hospitalized directly to participate in these programs, or rehabilitation is assigned to a patient who is already in hospital, hospitalized due to exacerbation. This clinical situation is more suitable for patients with marked deterioration and inability to do at home. The possible disadvantages of pulmonary rehabilitation in the hospital include a higher cost.

A review of the literature indicates significant progress in the study of pulmonary rehabilitation of patients with COPD. At the same time, the problem of recovery of physical abilities, which are significantly reduced in patients with COPD and are the main cause of their social maladjustment, remains unresolved.

A number of studies show that pulmonary rehabilitation in patients with COPD leads to a significant reduction in the number of hospitalizations and the number of days spent in hospital.

Physical training is the most affordable means of improving the condition of muscles in COPD and is regarded as the cornerstone of pulmonary rehabilitation [9, 10]. Conducting physical training is indicated for all patients with reduced exercise tolerance, shortness of breath, fatigue with exercise and restriction of daily activity.

In some studies, there were no positive effects from physical rehabilitation in patients with severe COPD, with severe shortness of breath, in other studies, by contrast, showed a significant improvement in exercise tolerance in this category of patients after exercise. Most of the studies on this problem have shown that the positive results of pulmonary rehabilitation do not depend on age, gender, history of smoking, pulmonary function. Berry M.J. et al. demonstrated that the results achieved in physical rehabilitation programs for patients with COPD of varying severity are comparable. Previously it was believed that patients with a mild disease do not need physical rehabilitation programs.

Nevertheless, it is known that the effect of pulmonary rehabilitation on the outcomes of COPD in patients with a progressive course of the disease is very limited, and timely lifestyle changes, which include maintaining the body's necessary fitness, optimal weight and muscle mass, quitting smoking, present significant potential for all-round influence on the patient's functional state and the rate of decline in pulmonary function. According to the recommendations of GOLD 2008, pulmonary rehabilitation, in which physical training is of primary importance, should be used in patients from the 2nd stage of the disease (moderate COPD), and according to GOLD 2011, at the stage A (mild severity) recommended physical activity. The data provided by E.B. Swallowetal. (2007), which demonstrate the dependence of survival of patients with COPD on the strength of quadriceps. Thus, it can be said that muscular strength is an indicator of the condition of a patient with COPD and predictions for the further course of the disease [13, 14].

Leg fatigue, in addition to shortness of breath, contributes to the reduction of physical tolerance of patients with COPD, and in some patients may be the main symptom. In one study, the effect of leg fatigue on exercise tolerance in patients with COPD after acute bronchodilation was studied. Despite the fact that the FEV1 indicator increased by 11% from the initial value, a significant increase in the endurance time did not occur, due to the fact that during exercise the tiredness of the leg muscles quickly developed.

Physical training programs are aimed at increasing the limited physical tolerance in a particular patient, the cause of which may be impaired ventilation and gas exchange, skeletal or respiratory muscle dysfunction [12]. Physical training, among other things, encourages patients to take an active lifestyle, improve the emotional background and the state of the cardiovascular system, and reduce the symptoms of the disease [15,16]. Improving skeletal muscle function as a result of training increases exercise tolerance even though there is no change in lung function. In addition, the increasing oxidative capacity of skeletal muscles leads to a decrease in alveolar ventilation with the same power of work. This can reduce dynamic hyperinflation and, therefore, shortness of breath on exertion [1].

Endurance training with the use of a bicycle ergometer or walking is the most common form of physical training in pulmonary rehabilitation [13]. The optimal mode is relatively long sessions with high load intensity (> 60% of maximum power) and a total effective training time of at least 30 minutes.

In chronic respiratory diseases, strength training is also effective. This type of training is better than endurance training, it increases muscle mass and strength. In a number of works, where only physical training of endurance was used in the programs of pulmonary rehabilitation of patients with COPD, an increase in endurance was observed to a greater degree than maximum working capacity. The dosage of training for endurance of muscles must necessarily take into account both the patient's feelings and the tolerance to his chosen regime. However, according to some data, there are no significant differences in the effectiveness of high or less intense training regimes.

The diaphragm in patients with COPD is adapted to chronic overload and is more resistant to fatigue. Despite this, with COPD, both the strength and endurance of the inspiratory muscle suffers, from which often leads to their weakness, diagnosed by measuring the maximum pressure during inhalation and exhalation. According to the literature, the addition of respiratory gymnastics to standard physical training in patients with COPD leads to better exercise tolerance than just physical training. [18].

According to literary data, about 20% of patients included in the pulmonary rehabilitation program with a course of physical rehabilitation, drop out prematurely. The state of weakness and soreness, shortness of breath and tired legs become significant barriers to physical rehabilitation. Therefore, the question of how to improve the tolerance of physical activity, which would increase the efficiency of pulmonary rehabilitation and the duration of the preservation of its results, remains relevant. Studies have repeatedly shown that the use of PR increases physical efficiency and facilitates shortness of breath, while no significant improvement in pulmonary function and impaired gas exchange in patients with COPD have been observed.

Dysfunction of the respiratory muscles plays an important role in limiting physical activity in patients with COPD, which determines the relevance of the issue of combining physical training with the training of respiratory muscles. The most commonly used types are respiratory muscle training, threshold load, inspiratory resistance, and normocapnic hyperpnoea. Diaphragmatic breathing, breathing through closed lips are additional methods for optimizing the ventilation function, both at rest and during exercise in patients with COPD. However, in some cases, diaphragmatic breathing can lead to increased work of breathing, increase inspiratory stress and shortness of breath.

In COPD, the appointment of respiratory gymnastics according to the methods of A.N. Strelnikova and K.P. Buteyko not very meaningful, due to the fact that the main indications for these methods are training solely inhaling and weakening the hyperventilation syndrome [19,20].

Patients with COPD with low weight, and not only among them, often have muscle atrophy associated with COPD, so simple screening should at least be a component of standard pulmonary rehabilitation [3]. The easiest way to do this is using body mass index (BMI), which is defined as weight in kilograms divided by height in meters squared. A BMI of <21kg / m2 is regarded as a lack of weight. Weight loss of> 10% in the last 6 months or> 5% during the month is also an unfavourable factor in the prognosis of the disease. However, prognostically more unfavourable is a decrease in lean (predominantly muscle) mass - less than 16 kg / m2 in men and less than 15 kg / m2 in women, which can be observed with normal and even overweight. Today, in this connection, the term “sarcopenia” is used instead of the concept “cachexia”. And it is the loss of muscle mass, and not a decrease in total body mass, some authors consider as indications for the active correction of physique disorders.

The loss of lean tissue mass in chronic obstructive pulmonary diseases can be determined by measuring the thickness of the skin fold, using bioimpedance analysis or using dual-energy X-ray absorptiometry.

There is evidence that the ratio of muscle strength to the mass of lean tissue of the extremities, expressed in kilograms, is the same in patients with COPD and controls, which confirms the theory that muscle loss is the main factor that determines the weakness of the limbs. Reducing the mass of lean tissue in COPD also leads to a decrease in the strength of the respiratory muscles.

In patients with COPD who are underweight, quality of life is reduced to a much greater degree than in patients with COPD with normal weight [23, 24]. In COPD, a relationship has been found between weight loss and increased mortality, regardless of the degree of airway obstruction.

Weight loss in patients with COPD may be caused by an increase in energy costs and an increase in metabolic activity or a decrease in the amount of food consumed. Anyway, the loss of muscle mass is a consequence of an imbalance between the synthesis and the breakdown of proteins. A decrease in the overall energy balance and protein metabolism can occur simultaneously, but it can also appear independently of each other due to dysregulation of metabolism. Increased metabolism may also be due to systemic inflammation in COPD.

Correction of nutritional status should be aimed at maintaining muscle strength with adequate protein and vitamins in the diet. Nutritional correction should initially consist in the correction of the patient's diet and the prescription of supplements rich in energy substrates.

In early controlled clinical studies, the prescription of oral liquid nutritional supplements without exercise restored the energy balance and increased body weight in patients with COPD with an initial weight deficit [25]. However, in most everyday situations, dietary supplements as monotherapy do not give a significant increase in body weight. The reason for this may be several factors, including a decrease in spontaneous food intake, a mismatch between nutritional supplements and the daily intake of food and physical activity of the patient, the presence of systemic inflammation. Given these factors, the inclusion of nutritional correction in standard rehabilitation programs should improve their results. In two controlled studies, it was demonstrated that nutritional supplements in a background of physical training under the supervision of a medical professional increased the body weight and weight of non-adipose tissue in COPD patients with weight deficit.

Patient education is one of the key components of standard pulmonary rehabilitation, despite the difficulties in assessing its direct contribution to the outcome of the disease. Education covers all aspects of pulmonary rehabilitation, from the time of diagnosis and continuing through the terminal stages of the disease.

Self- maintenance improves health and reduces the need for medical services for many chronic diseases. A recent, multicentre, randomized clinical trial confirmed that multi-component self-learning skills-oriented educational programs, including an exacerbation relief plan and home physical exercises, reduce the frequency of hospitalizations, emergency calls, and unplanned visits to the doctor and improve the quality of life. Treatment commitment is defined by WHO as the degree of compliance of a person’s behaviour with the recommendations of a health professional. Adherence to therapeutic methods of treatment is a crucial point in the management of patients with chronic respiratory diseases. The most effective methods that enhance adherence to treatment are aimed at improving the possibilities of self- maintenance of the patient. Irregularity of exercising and depression can predict low adherence to strength training programs at home [5]. Many studies show that in patients over 65 years of age, the educational level and previous physical training positively correlate with the regularity of training. It is known that the feeling of weakness and soreness were the most significant barriers to physical rehabilitation. One study showed that the progression of COPD and comorbid diseases are the most common obstacles to lifestyle changes in patients with COPD.

Patients with chronic respiratory problems are characterized by the appearance of anxiety, depression and other mental disorders.

Psychological and social support in the framework of pulmonary rehabilitation is important to ensure the adaptation of the patient's thinking and behaviour, attitudes towards his own disease. Patients with COPD often experience fear and anxiety associated with the expectation and appearance of dyspnoea.

This increased physiological readiness may cause or aggravate shortness of breath and general disability. Negative emotions from the disease, the inability to engage in familiar activities can be the cause of irritability, pessimism and aggressive behaviour in these patients.

Creating a system of adequate psychological support is an important component of pulmonary rehabilitation. Patients with chronic respiratory diseases receive a positive result from psychological counseling

on their concerns. Treatment of depression significantly improves the quality of life of such patients. At the same time, if moderate anxiety or depression can be resolved within the framework of pulmonary rehabilitation programs, then patients with significant psychological disorders should be referred to the appropriate specialist before rehabilitation.

In recent years, multidisciplinary rehabilitation has become the cornerstone of a general strategy for managing patients with COPD. At the same time, both in the world and in our country in this area there are a number of problems that need to be resolved as soon as possible. Pulmonary rehabilitation should be accessible to all patients who need it. This requires the training of health workers at all levels and the creation of a material base for rehabilitation activities. There is a need to create standards for pulmonary rehabilitation with the development of an optimal set of activities and the duration of their implementation. In addition, it is necessary to develop ways to preserve the effects of pulmonary rehabilitation, especially by improving the long-term "self-maintenance" and patient commitment to physical training at home.

REFERENCES

[1] Analysis of the levels of biomarkers of systemic inflammation, surfactant protein D and melatonin in COPD patients with varying degrees of airflow obstruction / Goncharenko O.V., Budnevsky A.V., Tokmachev R.E., Ovsyannikov E.S., Belov V.N. // Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2018; 9(5):1045-1049.

[2] Chronic heart failure in combination with the metabolic syndrome: optimization of medical and preventive measures / Tokmachev R.E., Kravchenko A.Ya., Budnevsky A.V. // System analysis and management in biomedical systems. 2017; 16(3):493-502.

[3] Chuchalin, A.G. Federal clinical guidelines of Russian respiratory society on spirometry / A.G. Chuchalin, Z.R. Aysanov, S.Yu. Chikin, // Pulmonology. - 2014. – (6). - 11-24. (In Russ.)

[4] Comorbidity of chronic heart failure and chronic Obstructive Pulmonary Disease: Peculiarities of Pathogenesis, Clinics and Diagnostics / Tokmachev, R.E., Mukhortova, M.S., Budnevsky, A.V., Tokmachev, E.V., Ovsyannikov, E.S. // Cardiovascular therapy and prevention. 2018; 17(6):62-68.

[5] Evidence for local platelet activation in pulmonary vessels in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease / C. Rostagno, D. Prisco, M. Boddi et al. // Eur. Respir. J. – 1991. – Vol. 4. – Iss. 2. – P. 147 – 151.

[6] Guzik, T.J. Vessel wall – where coagulation meets cell biology and immu- nology / T. J. Guzik, J. Dulak // J. Thromb. Haemost. – 2012. – Vol. 108. – Iss. 3. – P. 416 – 418.

[7] Budnevsky, A. V., Ovsyannikov, E. S., Labzhania, N. B. Chronic obstructive pulmonary disease concurrent with metabolic syndrome: Pathophysiological and clinical features// Terapevticheskii arkhiv.-2017; 89(1):123-127.

[8] Repine J.E., Bast A., Lankhorst L. Oxidative stress in chronic obstructive pulmonary disease//Amer J RespirCrit Care Med. – 1997. - 156: 341–57.

[9] Rhodes R.E., Martin A.D., Tawnton J.E. etal. Factors associated with exercise adherence among older adults: an individual perpective. Sports Med.- 1999. - 28: 397–411.

[10] Rochester D.F., Braun N.M. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. - 1985. - 132: 42–47.

[11] Sandford A.J., Weir T.D., Pare P. Genetic risk factors for chronic obstructive pulmonary disease // EurRespir J. - 1997. - 10: 1380–91.

[12] Siafakas, N.M. Optimal assessment of COPD /N.M.Siafakas, P.Vermeire, N.B.Pride // Europ. Respir. Rev. -1995. - Vol. 8. - P. 1398-1420.

[13] Shapiro S.D. The pathogenesis of emphysema the elastase- antielastase hypothesis 30 years later // Proceedings of AssocAmer Phys. – 1995. - 107: 346–52.

[14] Shoup R., Dalsky G., Warner S. et al. Body composition and healthrelated quality of life in patients with obstructive airways disease. Eur. Respir. J. – 1997. - 10: 1576–1580.

[15] Singer H.K., Ruchinskas R.A., Riley K.C. The psychological impact of end stage lung disease. Chest. – 2001. - 120:1246–1252.

[16] Snider G.L., Klenennan J., Thunbeck W.M., Benga. The definition of emphysema Report of a national and blood institute, division of lung disease.//Amer Rev Respir Dis. - 1985. - 132: 182–5.

[17] Spruit M.A., Gosselink R., Troosters T. et al. Resistance versus endurance training in patients with COPD and skeletal muscle weakness. Eur. Respir. J. – 2002. - 19: 1072–1078.

[18] Standford, A.J. Genetic risk factors for chronic obstructive pulmonary disease / A.J.Standford, T.D.Weir, P. Dp Pare//Eur. Respir.J. - 1997. - N10. - P.1380-1391.
[19] Stanescu D. Small airways disease and chronic obstructive pulmonary disease // Management of chronic obstructive pulmonary disease / Eds: Postma D.S., Siafakas N.M. The European Respiratory Society Monograph. – 1998. - 107–27.
[20] Sudakov O.V. The complex approach to the choice of the individual pharmacotherapy on the patiens chronic obstructive lungs disease and high blood pressure on the basis mathematical modelling// Systems analysis and management in biomedical systems. -2008; 7(2): 445-450.
[21] Steiner M.C., Barton R.L., Singh S.J., Morgan M.D. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomized controlled trial. Thorax. – 2003. - 58: 745–751.
[22] The possibility of non-pharmacological methods in increasing clinical efficiency of treating patients with chronic heart failure and metabolic syndrome / Tokmachev R.E., Budnevsky A.V., Kravchenko A.Ya. // Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2017; 8(6):832-839.
[23] The role of inflammation in the pathogenesis of chronic heart failure / Tokmachev R.E., Budnevsky A.V., Kravchenko A.Ya. // Therapeutic archive. 2016; 88 (9):106-110.
[24] Timens W., Coers W., van Straaten J.F.M., Postma D.M. Extracellular matrix and inflammation a role for fibroblast-mediated defective tissue repair in the pathogenesis of emphysema // EurRespir Rev. – 1997 - 7 (43): 119–23.
[25] World Health Organization. Adherence to longterm therapies: evidence for action. Annex. – 2003. - 1: 143.