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Why the drug treatment of COPD alone is not always accompanied by an improvement in exercise tolerance and patient's quality of life?.

Luev IA, Tokmachev RE*, Ovsyannikov ES, Shkatova YS, Liutikov YV[1], Naumkina DA[1].

Voronezh State Medical University, 10 Studencheskaya Street, Voronezh, Russia 394036
[1]Kursk state medical university.

ABSTRACT

According to clinical recommendations and generally accepted standards, the treatment of stable chronic obstructive pulmonary disease is accompanied by the use of inhaled glucocorticosteroids, bronchodilators, NSAIDs, mucolytic drugs [8, 17, 22]. However, the use of only drugs in the treatment of COPD is not enough, because this is not always accompanied by an improvement in exercise tolerance and in the patient's quality of life.

Keywords: COPD; chronic inflammatory process; antiproteinases; proteinases; systemic inflammation; exercise tolerance; quality of life.

Corresponding author

For a long time in the definition of COPD, both in foreign countries and in Russia, they inserted different meanings. Until the end of the 20th century, the term chronic obstructive pulmonary disease included a large number of diseases, different in both pathogenesis and clinical manifestations, which united only relatively reversible progressive obstruction of the respiratory tract - pulmonary emphysema, chronic bronchiolitis obliterans, severe forms of asthma, cystic fibrosis, pneumosclerosis, chronic pulmonary heart, pneumosclerosis (ICD №10, 2015). Each of the listed nosologies separately describes functional and morphological changes at different stages of the disease. The described principle has complicated epidemiological studies, the development of an adequate therapeutic approach and diagnostic criteria [1, 2, 25, 46]. The American Thoracic Association in 1995 proposed to treat COPD as a separate nosological unit [69]. To date, the main supporting documents for COPD are the Global Initiative for COPD (GOLD) and WHO (1998, 2003), which made it possible to isolate the concept of COPD from other nosologies previously included in it.

According to the global initiative for COPD (GOLD) in a revision dated 2018, chronic obstructive pulmonary disease is a progressive disease that is characterized by airflow limitation that is not fully reversible, and associated with an abnormal inflammatory response of the lung to noxious particles or gases. In many patients, comorbidities and exacerbation of the disease can affect the overall severity of COPD [1,2].

The main indicators on which the COPD classification was based until 2018 were functional indicators of the bronchopulmonary system conditions, based on the FEV1 values after bronchodilation. It was allocated 4 stages of the disease [3,4]. For mild severity, FEV1 was 80%, for moderate (stage II) 80–50%, for severe (stage III) 50–30%, for very severe (stage IV) <30%. The FEV1 / FVC ratio with any degree of severity remains <0.7.

When revising the GOLD document in 2018, the new classification of COPD was proposed, based on a comprehensive assessment of patient severity. The new classification takes into account, in addition to the severity of bronchial obstruction, based on the results of spirometric study, clinical data on the patient, such as the number of COPD exacerbations per year and the severity of clinical symptoms in accordance with the results of mMRC and the CAT test. [5].

Chronic obstructive pulmonary disease is a serious public health problem, characterized by a progressive increase in morbidity, loss of the working age population and high mortality rates worldwide. According to the World Health Organization (WHO), the prevalence of chronic obstructive pulmonary disease is 9.3 per 1,000 people among males and 7.3 per 1,000 people among females in the age group over 40 [6-8]. Progressing, COPD leads to temporary and permanent disability of the active part of the population, causing serious economic damage. According to statistics, on average, every year 3 million people die from chronic obstructive pulmonary disease in the world. WHO predicts that by 2020 the morbidity of COPD will increase and move from 12th to 5th place among all nosologies, and the death rate from this disease to 2-3nd place [9-11]. Today, according to official statistics in the Russian Federation, in our country there are about 1 million patients with COPD. However, in most cases, the detectability of patients at the initial stages of the disease development is extremely small and the largest percentage of patients with a first-time diagnosis of COPD are severe. According to the Russian Respiratory Society (RRO), there are about 11 million patients with COPD in Russia [12]. The results of one of the global studies (the BOLD project) made it possible to assess the prevalence of chronic obstructive pulmonary disease using standardized questionnaires and pulmonary function tests among people over 40 years old in developed and developing countries. They showed a reliable direct proportional increase in the incidence of COPD, depending on age [13-14]. The prevalence of COPD stage II and above (GOLD 2018), according to a BOLD study, was 10.1 ± 4.8% among the population in the age group of 40 years or more; in turn, for the male population - 11.8 ± 7.9% and for the female population - 8.5 ± 5.8% [15].

The disease develops as a consequence of the inflammatory process and degenerative-dystrophic changes in the bronchial mucosa due to the influence of various endogenous and exogenous factors, such as the long-term irritating effect of tobacco smoke, dust particles, allergens, respiratory infections, etc. The main pathophysiological criterion of bronchial obstruction is the reduction of the air flow rate due to the lesion of the bronchi and the combined destruction of the interalveolar septa of the pulmonary parenchyma. In this regard, the mechanics of respiration, ventilation and perfusion of various parts of the lungs are disturbed. The variability of the ratio of pathogenic links of the pathological process entails a variety of clinical symptoms of the disease.

The development of chronic obstructive pulmonary disease is caused by exposure to a variety of external and internal risk factors, but most researchers identify smoking as the main factor in the development of COPD in 80-90% of cases [16]. The composition of tobacco smoke includes many chemical compounds that have a direct pathogenic effect on the ciliated bronchial epithelium, which leads to a violation of the natural mechanism for the toxic substances and mucus evacuation from the lungs. This process, in turn, is a provoking factor for the development of bronchitis and emphysema. Irritation, aerosols, harmful gases, dust, especially containing silicon and cadmium, also leads to the development of COPD. Internal factors for the development of chronic obstructive pulmonary disease, chronic bronchitis and emphysema include α1 - antitrypsin deficiency, but among the total number of COPD patients, α1 - antitrypsin deficiency occurs in about 1% of cases[17].

The greatest role in the pathogenesis of COPD is played by oxidative stress, a chronic inflammatory process and an imbalance between antiproteinases and proteinases [18-21]. According to a number of authors, not only the structures of the pulmonary parenchyma and respiratory tract are involved in the process of inflammation, but also the vessels of the pulmonary circulation.

The key role in the inflammatory reaction belongs mostly to neutrophils, macrophages and T-lymphocytes. In the respiratory tract of patients with COPD, an increase of macrophages in the total number is observed due to a decrease in their apoptosis and increased migration of monocytes from the blood (Shpagina LA, 2013). The development of COPD is accompanied by an increase in the number of inflammatory cells, the so-called chemotaxis factors in response to increasing the concentration of inflammatory mediators, which leads to increased inflammation (proinflammatory cytokines) and structural changes (growth factors) [22]. Many authors agree that the transition of reversible airway obstruction into irreversible is determined by the relative balance of anti-inflammatory and pro-inflammatory cytokines, growth factors responsible for regulating their interaction, developing and attracting new immune cells to the area of inflammation.

Thus, inflammatory changes associated with the harmful effects of damaging factors of inhalation nature, lead to pathological disorders in the bronchi, changes in their elastic properties and changes in mucociliary clearance, as well as pathological changes in the pulmonary parenchyma. These processes lead to emphysematous restructuring of the lung tissue.

In the context of studying the pathogenesis of COPD, we cannot ignore the changes in the vessels of the pulmonary circulation. It is worth noting that today the role of the vascular component in the development of chronic obstructive pulmonary disease has not been fully established. In his studies, Voelkel N.F. et al. draws attention to a violation of the of endothelial factors synthesis, which is accompanied by increased thrombotic activity and the formation of pulmonary microthrombosis in patients with COPD. In turn, Palange P., Sprunger D.B., Boschetto P. et al. in their studies provided data on the peculiarities of thrombogenesis in patients with COPD. They suggested that damage to the endothelium by neutrophilic elastase may be one of the links in the pathogenesis of chronic obstructive pulmonary disease. Kerr J.S., et al. in 1985, during experimental work on rats, he proved that blockade of vascular endothelial growth factor (VEGF) is accompanied by the development of emphysema.

It is well known that chronic obstructive pulmonary disease is accompanied by many extrapulmonary manifestations of the disease, which is due to the systemic effect of chronic inflammation. One of the leading extrapulmonary manifestations is impaired function of peripheral skeletal muscles, which leads to a decrease in exercise tolerance. Dyspnea as one of the manifestations of COPD is considered to be the main cause of decreased exercise tolerance. Progressive dysfunction of skeletal muscles is associated with a decrease in the number of contractile proteins and mitochondrial disorders, but this process is aggravated by other factors, such as systemic inflammation, pathological disruption of normal gas exchange, oxidative stress, corticosteroid therapy, a sedentary lifestyle [23]. To assess the general state of the muscular system of patients with COPD, the functional status of the quadriceps of the thigh is most often examined. S. Bernard et al, in the course of their research, evaluated patients with COPD of the cross-section area and force m. latissimus dorsi and pectoralis major, as well as m. quadriceps femoris (age - 66 ± 7 years, FEV1 - 44 ± 14%). As a result of the study, it was found that the reduction in the strength of the quadriceps femoris in patients with COPD was 28%, and the reduction in the strength of the muscles of the trunk was 15-16% compared with the control group. Also in patients with COPD, the cross-section area of the skeletal studied muscles was reduced by 30% compared with the control.

Reduced exercise tolerance in patients with COPD is closely associated with impaired gas exchange, impaired respiratory muscle function, and limited ventilation. The disease is often accompanied by the development of hyperinflation, which indirectly creates unfavorable conditions for the muscles involved in the act of breathing. In chronic obstructive pulmonary disease, a progressive decrease in the strength and endurance of the inspiratory muscles is observed, which in turn impairs the patient's physical ability due to exacerbation of hypercapnia,desaturation of blood at night and shortness of breath. In studies, morphological changes in the respiratory muscles depend on the severity and stage of respiratory failure (Platonova IS, 2004).

The development of the pathological process in COPD is often accompanied by a decrease in the nutritional status of patients. In patients with mild and moderate stages of COPD, a decrease in body weight is observed in 10-15% of cases, while in patients with severe stages of COPD, a decrease in body weight is observed in 50%. The most pronounced decrease is in muscle mass, while the decrease in fat mass is negligible [12, 19].
The study of the effects of statins in COPD patients is also of great interest. It is well known that statins reduce the cholesterol concentration by inhibiting HMG-CoA reductase [6]. This mechanism is what the use of statins in treatment of atherosclerosis is based on. But statins also affect mechanisms of immune activation and regulation leading to a decrease in the production of proinflammatory cytokines, chemokines and adhesion molecules and, as a result, to a decrease in systemic inflammation [20]. This anti-inflammatory effect may have a beneficial effect on the course of cardiovascular pathology but it is not yet clear what role it plays in the treatment of COPD [3]. The results obtained by F.J. Frost et al. demonstrated a reduced risk of death in patients with COPD that received statins at a dosage of ≥4 mg/day. In turn, van Gestel and et al. studied the effect of statins on mortality in 3371 cardiovascular surgery patients, 1310 of which had COPD. The data they obtained showed a decrease in both short-term (30-day) and long-term mortality by 52% and 33% respectively [24]. At the same time, short-term mortality decreased with the use of standard doses of statins only, and long-term mortality was reduced by the use of statins in both standard and low doses. Although the data obtained are rather promising, it is worth remembering that only cohort and retrospective studies have been carried out so far, therefore further research may be necessary to better address this issue.

According to clinical recommendations and generally accepted standards, the treatment of stable chronic obstructive pulmonary disease is accompanied by the use of inhaled glucocorticosteroids, bronchodilators, NSAIDs, mucolytic drugs [1, 8, 17, 22]. However, the use of only drugs in the treatment of COPD is not enough, because this is not always accompanied by an improvement in exercise tolerance and in the patient's quality of life. Therefore, the development and application of non-pharmacological methods that reduce systemic inflammatory response, improve the course of chronic non-communicable (noninfectious) diseases, such as COPD, and the quality of patients life are so important today [3, 20, 21].

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