Central Asian Journal of Medicine

Volume 2019 | Issue 2 Article 1

6-23-2019

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Article info

Published: june 2019 y

Key words: *ischemic heart disease, chronic obstructive pulmonary disease, risk factors*

ABSTRACT

The purpose of literature review is analytical analysis of the prevalence of ischemic heart disease in the patients with COPD. In this article there is noted significance of the subject area. There are presented detailed data about possible causes for development of this comorbid state, described literature data about possible common pathogenic mechanisms and risk factors. It is emphasized that cardiovascular risk increasing in the patients with COPD, with elevation of severity of disease, growing of the exacerbation frequency. In the rather complete volume there are presented information about role of endothelial dysfunction, chronic systemic inflammation and the system of coagulation and anticoagulation as common pathogenic mechanisms providing development of myocardial infarction in the patients with COPD in this article.

Today, chronic obstructive pulmonary disease (COPD) is one of the most common noncommunicable diseases in the world, and is the third leading cause of death in the world after stroke and coronary heart disease (CHD) [14].

The number of patients with COPD is growing every year, especially in developing countries, and therefore one of the main problems of modern medicine is timely treatment, improving the quality of life and reducing mortality among this group of patients.

According to a scientific study conducted in the French population, out of the 4237 patients with COPD (with average age 68 years, 55% men, with annual mean mortality 4.9%), the following common comorbide conditions were detected: 68.7% had cardiovascular diseases, 15.2% diabetes, 14.2% depression and 10.6% cancer. The authors concluded that the most common comorbide condition for COPD is cardiovascular diseases, which occur in more than two thirds of patients with COPD, mortality in this group is one of the highest as well, ceding only to cancer [19].

According to a number of scientific studies, the frequency of combinations of COPD and CHD is quite high: 48% among patients with COPD and up to 62% among patients with CHD, and the mortality rate at their combination reaches 50% and more [34].

64% of patients with COPD have coronary atherosclerosis as a comorbide pathology [43,33].

A large number of scientific studies have been devoted to studying the interinfluence of these diseases, and so far little is known about the prevalence, extent, and basic mechanisms of cardiovascular risk in patients with severe and extremely severe COPD.

The presence of CHD in patients with COPD negatively affects health, symptoms, tolerance to physical exertion, recovery time after recrudescence, hospitalization frequency and mortality.

As a result of population studies, it was found that the risk of cardiovascular mortality is 2-3 times higher among patients with COPD and amounts to approximately 50% of the total number of fatal casualties [32], as a consequence of cardiovascular catastrophes this is one of the leading causes of death for patients with COPD along with pulmonary embolism [15,18,23,28].

It is interesting that risk of cardiovascular accident is especially high after recrudescence in patients with COPD [8].

So, in patients with COPD, who have 5 and more recrudescences within a year, the risk of myocardial infarction increases approximately 5 times. Attack phase is the factor, which provokes the development of myocardial infarction (MI), and is the trigger of severe coronary events in patients with COPD. However, the data on which particular categories of patients with COPD have the greatest risk of developing MI and for what reason is not enough in the literature. It is only known that an increase in the risk of MI affected by COPD can be associated with an additional load on hemodynamics with the increase of cardiac function, an increase in pressure in the pulmonary artery, an increase in the work of the respiratory muscles, an increase in the activity of the sympathoadrenal and renin-angiotensin-aldosterone systems, as well as with the release of proinflammatory cytokines from the focus of inflammation into the systemic circulation [31,37].

The effect of inflammation on the myocardium is indicated by subclinical myocardial damage (increase of arterial stiffness and increase in the number of biomarkers of myocardial injury) in patients with frequent recrudescence of COPD, which may also be associated with respiratory tract infection and inflammation [28,29].

According to modern concepts, behind the pathogenesis of both CHD and COPD lies the systemic inflammation involving pro-inflammatory cytokines and C-reactive protein (CRP), which play a key role in the development of the immuno-inflammatory process, and contribute to the accumulation of free radicals, which lead to atherogenic lipid changes, stimulate the production of acute phase proteins, increase activation and adhesion of cellular elements.

Since the recrudescence of COPD is indubitably accompanied by an increase of systemic inflammatory dislocations, we can assume a more pronounced structural-geometric rearrangement of the heart in the case of myocardial infarction in the phase of recrudescence of bronchopulmonary pathology. It was found that asymptomatic myocardial injury is often found in moderate exacerbations of COPD, which is due to a longer period of recuperation in this type of exacerbation [28].

This hypothesis is supported by evidence of an increase in biomarkers of myocardial injury and dysfunction in patients hospitalized due to recrudescence of COPD, an increase of these biomarkers is recognized as an independent predictor of fatality rate [4,25].

According to a study devoted to the definition of troponin and the calculation of the death risk with its increase, it is indicated that even asymptomatic small reinforcements

in the concentration of troponin in serum can increase the risk of death by 2 times. So in patients with COPD with a troponin concentration of less than 0.014 μg / L and 0.014-0.04 μg / L, the relative risk (95% CI) of death made 4.5 (1.2-16.0), while in patients with a concentration of more than 0.04 μg / l risk equalled 8.9 (2.4-32.0) [16].

A moderate increase in troponin in patients with recrudescence of COPD determined at the outpatient stage was 29.7% and 12.7% of the increased troponin content, while in patients hospitalized into the inpatient facilities with severe recrudescence of COPD, these rates were from 37.4% and 36.4% [12].

Prospective studies indicate that high levels of mediators of inflammation in the blood plasma are reliable and independent predictors of myocardial infarction in healthy individuals, as well as overall fatality rate in older men and women. On the other hand, it is known that with a steady course of COPD, the levels of these inflammatory markers are also increased, which is reflected in the presence of a direct correlation between the severity of COPD and concentrations of CRP, TNF-α, IL-6 and a number of other pro-inflammatory cytokines [10].

With the recrudescence of COPD, their levels increase 2.5–3 times, and, therefore, each recrudescence is associated with an increased risk of new cardiovascular events [36].

There are hypotheses that the main influence on the development and progression of coronary artery atherosclerosis is caused by systemic inflammation in COPD, which is mediated by a high level of inflammatory mediators both in exacerbation of COPD and in the period of remission [12,35].

The common pathogenetic mechanisms of COPD and CHD are numerous. Several mechanisms lie on the basis of this process: tachycardia, the procoagulant state of the coagulation system and the presence of active systemic inflammation, high arterial stiffness of the vessels, and also supposedly administration of systemic glucocorticosteroids [20, 27, 42, 44]. As it is known, hypoxia, developing with chronic wheeze in conditions of insufficient oxygenation, contributes to an even greater increase in myocardial oxygen demand and further deterioration of microcirculation [38,40]. Besides, the progression of hypoxia leads to the increase in the threshold of pain sensitivity and the formation of painless myocardial ischemia, similar to that in patients with diabetes [11].

A number of studies indicate the presence of increased arterial stiffness in patients with COPD in a direct correlation with the frequency of recrudescence, regardless of age, gender, and concomitant CHD. The authors also point to a direct relationship between arterial stiffness of vessels and the level of serumal C reactive protein in patients with steady COPD [2]. Increase of arterial stiffness of the vessels leads to more intensive work of miocardium, increases systolic blood pressure and lowers diastolic blood pressure, thereby reducing coronary blood flow [45].

The mechanisms underlying the relationship of respiratory tract infection, systemic inflammation, increased arterial stiffness, myocardial injury at COPD have not yet been fully studied, but may also include hyperactivity of the sympathetic nervous system, endothelial dysfunction of the main arteries and reduced bioavailability of nitric oxide [2].

If with stable COPD it is not considered that arterial stiffness is caused by endothelial dysfunction [21], then with recrudescence of COPD this relationship is difficult to deny [22].

Endothelial dysfunction at the combination of COPD with CHD is more signified than with monopathology and, in our opinion, can be not only a consequence, but also a cause of the development of this comorbide pathology [30].

COPD and CHD have common risk factors such as smoking, urbanization, low physical activity, population aging, genetic disposition, with both pathologies, inflammation occurs as a common pathogenetic mechanism [1,6,11,13].

The presence of common risk factors, as well as general mechanisms of the pathogenesis of COPD and CHD, namely systemic inflammation, requires further deeper study of the clinical course and content of inflammatory markers in patients with CHD in combination with COPD in order to optimize diagnosis and treatment.

In addition, society has serious social prerequisites for the simultaneous development of the indicated diseases: the widespread distribution of smoking, air pollution by various pollutants, stress factors, inadequate physical activity, malnutrition.

By analyzing the provided data, it can be concluded that patients with COPD have a high risk of developing myocardial infarction due to hypercoagulation changes, especially after severe recrudescence of COPD.

The course of the combined pathology is characterized by certain clinical features and an dismal prognosis. Therefore, the main task of the doctor at the stage of diagnosis - is the early detection of the diagnostic criteria of CHD in a patient with COPD. Diagnosis should be purposeful and carried out using additional research methods.

Patients who have an association of COPD and CHD belong to the category of “difficult patients”, they are usually middle aged. Deep knowledge of the advantages and disadvantages of the medications used is required for their effective treatment.

Beta-blockers have been contraindicated for patients with COPD for a long time. COPD has often been the cause of the inability to treat patients with CHD and cardiac decompensation with beta-blockers [39,41].

The reason for the prohibition of prescribing this group of drugs to patients with COPD was that when they are prescribed, not only β1-adrenoreceptors, which provide antihypertensive and cardio protective effects, are blocked, but also β2-adrenergic receptors, which cause a spasm of medium and small bronchus. Deteriorating lung ventilation can lead to the rapid development of hypoxemia and is clinically manifested by increased respiratory embarrassment of breath and rapid breathing. The advent of highly selective β1-adrenergic blockers, which don't have adverse effects caused by blockade of β2-adrenergic receptors, has made possible the appointment of beta-blockers in clinical practice [26].

Considering the antianginal, cardioprotective, antihypertensive, antiarrhythmic properties of beta-blockers, the treatment of CHD and cardiac decompensation in patients with COPD with the drugs of this group is advisable, in total control of possible adverse effects [7,39,41].

Bisoprolol, nebivolol, carvedilol, metoprolol succinate have a proven ability to prevent untimely death in various clinical situations. Bisoprolol and metaprolol can be used for stable COPD [15].

Ekstrom MP and others [9] have estimated the increase of fatality in patients with heavy oxygen-dependant COPD, who received beta-blockers.

In the other study, which included 35 082 patients with recrudescence of COPD, who continued to take beta 1-selective beta-blockers for CHD prescribed earlier, cardiac decompensation or hypertension, there was not found any increase of the

mortality. This is important because the risk of developing cardiovascular events increases after or during the recrudescence of COPD. [8,39].

It is known that bisoprolol, nebivolol, metoprolol succinate when administered to patients with COPD within the period of up to a year were safe and did not cause adverse effects.

Inhibitors of angiotensin converting enzymes (ACE inhibitors) have a number of positive properties: arterial vasodilation, nephro-, cardio-, angioprotective effect, reverse development of myocardial remodeling, vascular wall. Reducing the release of aldosterone is accompanied by an increase in the excretion of sodium and water, an increase in the level of potassium in the blood plasma.

Given the fact that ATE inhibitors have the quality of reverse remodeling of myocardium, cardio-, nephro-, angioprotective effects, lead to arterial vasodilation, the use of this group of drugs in patients with COPD for the correction of systolic dysfunction of the left ventricle, arterial hypertension, acute myocardial infarction for hemodynamic discharge secondary prevention of cardiovascular disasters is appropriate. The use of inhibitors of angiotension-converting enzyme (ACE) inhibitors in COPD has served for reduction of the number of recrudescence and fatality rate among patients in this group [3,24].

Indications for the administration of ACE inhibitors in patients with the association of COPD and CHD are: the signs of hypertrophy and dilatation of the myocardium of the right and left ventricles in combination with pulmonary hypertension; anterior myocardial infarction; сердечная недостаточность of III - IV degr. according to NYHA; arterial hypertension. At the same time, the principle of dose titration from minimum to optimal is used under the control of the patient's state of health and external respiration function. The importance of conducting an acute sensitivity test to ACE inhibitors increases [5].

Statins have proven their effectiveness in the treatment of patients with CHD and cardiac decompensation due to the pleiotropic effect. Statins have anti-inflammatory, immunomodulatory, antioxidant effects and decrease the level of cholesterol. [41].

A direct correlation between the use of statins in patients with COPD and a decrease of the fatality rate from all causes, a decrease in the level of C reactive protein, a decrease in the risk of recrudescence and an improvement in the quality of life of patients is observed in many studies [17,46].

Blockers of slow Ca-channels have antianginal, antiarrhythmic, antihypertensive, antiatherosclerotic, organo-protective actions. They contribute to the reverse development of myocardial hypertrophy and are comparable in this effect with ACEI. The combination of such properties with good tolerance, the lack of significant interaction with other medicines makes them very useful in cardiology practice. It should be noted that long-term administration of short-acting dihydropyridine - nifedipine - contributes to the increases of the mass of the left ventricle and increases the fatality rate.

"Short" nifedipine in patients with COPD and CHD is used limitedly, mainly as an ambulance for increasing blood pressure [5].

Nitrates are used for treatment of almost all forms of CHD. The presence of articulated antianginal activity allows prescribing these drugs for the prevention and relief of episodes of pain in patients with stable effort angina. When they are taken, the tolerance of physical activity increases significantly, the number of angina attacks decreases.

Prevention of thrombotic complications with antiplatelet agents is the main indication for the appointment of aspirin in patients with cardiovascular disease.

Aspirin is used in doses from 50 to 325 mg / day, affecting the cyclooxygenase-1 of the thrombocytes, as a result of blocking of which the production of thromboxane A2 is almost completely stopped. Other antiplatelet drugs serve only as complement to aspirin.

Clopidogrel is the second in the list of medications by the quality of antiplatelet action after aspirin, its mechanism of action is the blockade of ADP receptors on thrombocytes, which in turn reduces their aggregation properties.

In patients with COPD, aspirin can provoke the wheeze by blocking cyclooxygenase and directing the metabolism of arachidonic acid towards the formation of leukotrienes. However, in the absence of these signs, the drug can be prescribed to patients with COPD and CHD in the minimum effective antiplatelet doses (75 mg) under the control of the state of health and respiratory function. If the patient's condition worsens and this is not explained by anything other than taking aspirin, the drug is canceled. The choice in this case is clopidogrel.

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