EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CORONARY ATHEROSCLEROSIS

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ABSTRACT

Despite the fact that coronary heart disease (CHD) as a separate nosological unit has been well studied, there are numerous and not so developed aspects of the problem associated with a combination of CHD and other concomitant diseases. If the aggravating contribution of diabetes mellitus (DM) or chronic kidney disease (CKD) in relation to the immediate and long-term prognosis of patients with coronary heart disease is described in detail and reflected in the latest edition of the European Recommendations on Revascularization (2014), then for COPD, the accumulation of scientific data on its clinically significant relationships continues with CHD, COPD is not yet included among the predictors in mathematical models for calculating cardiovascular risk, but this may happen in the near future.

Key words: coronary heart disease (CHD), chronic kidney disease (CKD), diabetes mellitus (DM)

Introduction

The prevalence of COPD exceeds that for diabetes and CKD, and among the causes of death by 2020, it will take its place in the world. It has been found that COPD patients are more likely to die from cardiovascular causes than from the COPD, and among them the leading place is occupied by coronary heart disease. The morphological substrate of coronary artery disease is atherosclerotic plaque (ASP), and published a large number of papers in which the authors evaluated and compared the degree of atherosclerotic lesions of the coronary arteries in patients with coronary artery disease and COPD using multispiral computed tomography of the heart and invasive coronary angiography (CAG). In general, patients COPD revealed a more severe atherosclerotic lesion in comparison with control groups without COPD. However, in almost all of these publications, scales were used that quantitatively generalize all ASBS in the coronary arteries of one patient and do not allow to identify

any features of coronary atherosclerosis, thanks to which, perhaps, an unfavorable prognosis scenario is realized in patients with a combination of coronary heart disease and COPD. Some authors are trying to establish a link between the severity of atherosclerotic lesions and the severity of COPD according to the traditional classification. However, in the latest editions of the Global COPD Initiative (GOLD, 2014) admits the failure of attempts to classify COPD based only on a single spirometric indicator (in particular, the volume of forced exhalation in 1 second (FES1)). This classification is largely formal, since patients, attributed by her to one gradation of severity, they often differ greatly in their condition. It has been repeatedly noted that even within the same severity of the disease in patients with COPD (for example, severe, with FES1 in the range of 30-50% of the proper values), there is a wide variability of clinical manifestations: from complete absence of symptoms to a pronounced decrease in quality of life, exercise tolerance and self-care ability. The most important factor dramatically accelerating the rate of decline FES1 and approaching the onset of severe and extremely severe COPD, are exacerbations.

Exacerbation of COPD is understood as a condition characterized by worsening of respiratory symptoms that goes beyond their daily fluctuations and can lead to a change in the mode of therapy used. According to the results of a large (n=2138) study ECLIPSE has identified a special phenotype of the disease, the criterion for which is frequent exacerbations (2 or more per year), and this is how it differs from other COPD phenotypes.

According to G. Donaldson, exacerbation of COPD is associated with a more than twofold increase in the risk of developing MI in the first five days after exacerbation. Thus, patients belonging to the phenotype with frequent exacerbations represent the most vulnerable category of COPD patients not only in terms of the likelihood of further exacerbation of respiratory symptoms, but also have a more unfavorable long-term prognosis in terms of cardiovascular events than other patients with COPD. In this regard, in our opinion, a detailed assessment of atherosclerotic lesions of the coronary bed in these patients in comparison with other patients with COPD is of interest.

Material and methods

110 patients with COPD who underwent PCI for acute coronary syndrome (ACS) in 2012-2014 were included in the study, which was simultaneous in design. Within 24 hours from the moment of admission to the hospital, the patient was diagnosed with a clinical diagnosis – "Q-positive MI", "Q-negative THEY" or "unstable angina". To do this, the concentration of troponin-I in the blood was evaluated and an electrocardiogram. The diagnosis of "acute MI" and "unstable angina" was established according to the criteria of the European Society of Cardiology (2011, 2012). Inclusion criteria: age ≥40 years; smoking at the time of admission or cessation of smoking no

more than 1 year before hospitalization; smoking history ≥10 pack-years; ACS with the final diagnosis of "myocardial infarction" (MI) or "unstable angina"; PCI with stenting (holometallic or drug-coated stent) with complete restoration of blood flow in the infarct-related artery within 24 hours from the onset of symptoms leading to hospitalization, without angiographic signs of residual stenosis, dissection or distal embolization; COPD diagnosed in accordance with the GOLD 2011 criteria, according to which the post-bronchodilation value FES1, attributed to the value of the forced vital capacity of the lungs (VCL), should be less than 0.70, and the severity of the disease is determined based on the value of FES1. Exclusion criteria: heart defects in the presence of indications for their surgical correction; coronary artery bypass grafting (CABG) or PCI anamnesis; bronchial asthma; active tuberculosis; interstitial lung diseases; idiopathic pulmonary arterial hypertension; pulmonary thromboembolic disease; systemic connective tissue diseases; malignant neoplasms; thoracotomy with a history of lung resection; development of complications during PCI: dissection, perforation or rupture of the coronary artery, noreflow phenomenon; left ventricular ejection fraction (LVEF) less than 35% by the end of the 1st week after revascularization, refusal of the patient from participation in the study.

In accordance with the definition of exacerbation by GOLD 2011, the number of exacerbations of COPD in the year preceding inclusion in the study was estimated. All patients underwent spirographic examination according to the recommendations of the American Thoracic Society

(2005), as well as a bronchodilation test with salbutamol at a dose of 400 mcg.

CAG was performed on an angiographic device AXIOM of Siemens (Germany) according to the standard methodology of M.Judkins. The description of the obtained angiograms was carried out with a detailed segment-by-segment analysis of atherosclerotic lesions.

Type of left ventricular myocardial blood supply (left, right or balanced) was determined depending on the location of the posterior descending artery. With the right type of myocardial blood supply, 9 main segments were distinguished – the trunk of the left coronary artery, the proximal, middle and distal segments of the anterior interventricular artery and the right coronary artery, the proximal and distal segments of the envelope artery. With the left type of blood supply, 9 segments were also distinguished: proximal, middle and distal segments of the anterior interventricular artery and envelope arteries and 2 segments (proximal and distal) for the right coronary artery. The defeat of second-order branches was taken into account separately. Coronary artery stenoses were divided into hemodynamically insignificant (less than 50% of the vessel diameter) and hemodynamically significant (from 50% to 95% of the vessel diameter). In addition, stenosis over 95% but less than 100% of the vessel diameter were isolated as critical (subocclusions), and 100% stenoses as occlusions.

Took into account the character lesions (diffuse, extended). Depending on the presence of hemodynamically significant stenoses in the large coronary arteries (anterior descending, envelope and right coronary), the lesion was described as one-, two- and three-vessel. In addition, the number of points on the SYNTAX scale was determined using an online calculator. The concentration of CRP in the blood was determined by highly sensitive immunoturbidimetry with latex enhancement on a repeat visit 1 month after discharge from the clinic without exacerbation of COPD.

Statistical analysis was performed using programs STATISTICA 10.0 for Windows. The measure of the central tendency for continuous variables with a distribution close to normal was the arithmetic mean M, with significant deviations from the normal distribution, the median Me. The measure of the spread, depending on the type of distribution, was the standard deviation SD or the interquartile range [Q1; Q3]; percentages were used to describe the shares.

The Shapiro–Wilk criterion was used to assess the normality of the distribution. The nonparametric Mann–Whitney criterion was used to assess the differences between the two groups, the criterion Kraskel –Wallis – when comparing more than two groups. To compare the fractions, the exact Fisher criterion and the chi-square criterion were used. All statistical criteria were applied in the form of their bilateral variants. Spearman's method was used to study the correlation. $P < 0.05$ was taken as the threshold level of statistical significance.

Results

Depending on the presence of two or more exacerbations of COPD in the previous year, two groups of patients were identified. The groups did not differ in age, gender, the presence of concomitant diseases such as hypertension, CKD and diabetes mellitus, as well as in the presence of a history of previous MI.

There were also no statistically significant differences in the concentration of total cholesterol and its fractions in the blood. However, the level of CRP was significantly higher in the COPD group with a history of frequent exacerbations, which indicates the activity of persistent inflammation in these patients, even without exacerbations. The relationship between belonging to the COPD phenotype with frequent exacerbations, we have established a number of features,

The total number of all stenoses, hemodynamically significant stenoses and occlusions/critical stenoses was higher in the group with frequent exacerbations: 26%, 37% and 47% higher, respectively, than in the group without frequent exacerbations. The main contribution to the formation of these differences was made by hemodynamically significant stenoses of the main branches of the CA, localized in the proximal and distal segments (the difference between the groups 31% and 87%, respectively), as well as stenosis of branches of the 2nd order (54% difference). The traditional assessment of the severity of coronary lesions by dividing into one-, two-

and three-vascular lesions did not reveal statistically significant differences between the groups, including due to the lower sensitivity of statistical criteria assessing differences between

the lobes. The score on the SYNTAX scale found differences between the groups, but the difference was less than 4 points, which can hardly be considered significant. At the same time, the vast majority of patients (91.7, respectively% and 96.5%) in both groups had less than 23 points, which allows them to be attributed, from the point of view of this scale, to the same risk category of long-term adverse cardiovascular events. The severity of COPD according to the GOLD classification had a weak correlation with the total number of all CA stenoses (r=0.19; p<0.05), and there was no correlation with the total number of stenoses of the main branches of the CA. At the same time the concentration of CRP in the blood, reflecting the severity of chronic persistent inflammation was associated with the severity of coronary atherosclerosis, and the closest correlation was found between the concentration of CRP and the total number of coronary stenoses (r=0.36; p<0.001), as well as between CRP and the total number of stenosis of the main branches of the CA (r=0.36; p<0.001). The correlation between the number of points on the SYNTAX scale and the concentration of CRP was weaker, the level of statistical significance was lower (r=0.29; p<0.01), and there was no correlation of points on the SYNTAX scale with the severity of COPD.

Discussion

A common reason for combining suffering that is very heterogeneous from a clinical point of view into one nosological unit, called "COPD", is, firstly, a persistent restriction of the air flow velocity detected by spirography and having a tendency to progress, and, secondly, an unusual inflammatory response of the lung tissue to the action of pollutants.

Most of the work on the evaluation of the relationship between CHD and COPD considers the population of patients COPD as a whole, at best using spirographic gradation of degrees of severity, reflecting only the first aspect of the nosological definition of COPD. The second aspect, which characterizes COPD as a separate nosology, is practically not taken into account in studies of cardiovascular pathology. However, it may have the greatest impact on the risk of developing diseases associated with atherosclerosis, since systemic inflammation plays a significant role in the development and progression of atherosclerosis. Exacerbation of COPD causes an escalation of the systemic inflammatory response characteristic of this disease.

Patients belonging to the COPD phenotype with frequent exacerbations, in our study, there was generally a more severe lesion of the coronary bed, which, however, was not reflected in its traditional characterization as one-, two- or three-vascular. This classification of the severity of the lesion was used in most scientific papers in which CAH analysis was performed, however, a unified approach to the above division has

not been formulated: some researchers keep track of the number of arteries requiring revascularization, others – by the number of arteries with hemodynamically significant stenoses. There is a situation in which the same CAG can be interpreted in different ways.

The SYNTAX scale is intended not so much to characterize the lesion of the coronary bed, as to assess the long-term prognosis, as well as to make a decision on the method of revascularization.

Patients with severe exacerbations of COPD had only a slightly higher score on the SYNTAX scale, however, the proportion of patients belonging to the lower third on this scale (0-22 points) was almost the same as in the comparison group. Prevalence of patients in the range 0-22 on the scale SYNTAX in our study is associated with at least two circumstances. Firstly, for most patients, this episode of ACS turned out to be the debut of coronary heart disease and, thus, they did not have a long history of the disease. Secondly, we did not include in the study those patients in respect of whom a council of specialists decided to carry out planned CABG as the next stage of revascularization after PCI on an infarct-related artery.

Detailed segment-by-segment description of each major epicardial coronary artery taking into account all the detected stenoses, their hemodynamic significance and extent, it allows, in our opinion, to form the most complete picture of the severity and prevalence of coronary lesions and explain the increased risk of cardiovascular events (cardiovascular death, myocardial infarction, stroke, repeated revascularization) in COPD patients with frequent exacerbations in the long-term period after carrying out PCI. A similar approach to the description of the lesion of the spacecraft was also used in other works.

For example, an increase in the total number of all stenoses, regardless of their hemodynamic significance, may eventually lead to the need for repeated revascularization due to the growth of those plaques that were hemodynamically insignificant at the time of CAG. On the other hand, destabilization and rupture of a small plaque causes the formation of a blood clot in the lumen of the coronary artery, which underlies the development of ACS, and can also lead to cardiovascular death. An increase in the number of hemodynamically significant stenoses in patients with frequent exacerbations COPD in comparison with patients without exacerbations may have a consequence in the future in the form of the development or progression of angina pectoris and, as a result, repeated PCI or CABG. According to our data, belonging to the COPD phenotype with frequent exacerbations is also accompanied by an increased frequency of extended stenoses and distal lesions of the coronary bed, which, firstly, may complicate revascularization, and secondly, worsen its long-term results. Exacerbations of COPD are accompanied by an increase in systemic inflammation, an increase in blood levels of CRP, fibrinogen and interleukin-6, which

can directly or indirectly lead to increased thrombosis, as well as the likelihood of rupture of atherosclerotic plaque. Our data on the difference between the level of CRP in COPD patients belonging to the phenotype with frequent exacerbations, but in a stable condition, and in COPD patients without a history of frequent exacerbations suggest that the named COPD phenotype is characterized by a higher background level of inflammation, which may predispose to more aggressive course of coronary atherosclerosis. Indirectly, this relationship is confirmed by the found positive correlation between the level of CRP and the severity of coronary atherosclerosis.

Conclusions

The presence of COPD phenotype with frequent exacerbations in ACS patients is associated with more severe damage to the coronary bed due to an increase in the total number of stenoses, hemodynamically significant stenoses, as well as occlusions and critical stenoses. The main contribution is made by hemodynamically significant stenoses localized in the proximal and distal segments of the coronary arteries, as well as in the branches of the 2nd order.

Lesions of the trunk of the left coronary artery and the middle segments of the main coronary arteries were not associated with the COPD phenotype with frequent exacerbations. This phenotype is accompanied by an increase in the frequency of extended stenoses.

A more severe coronary lesion in these patients may be based on chronic persistent inflammation, the degree of which reflects the increased level of CRP characteristic of these COPD patients even in a stable condition.

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