DOI: 10.20514/2226-6704-2020-10-2-131-138

N. Yu. Grigoryeva, T. P. Ilyushina, K. S. Kolosova*, N. B. Koroleva, A. A. Streltsova, D. V. Solovyeva

Federal State Budgetary Educational Institution of Higher Education «Privolzhsky Research Medical University» of the Ministry of Health of the Russian Federation, Nizhny Novgorod, Russia

Clinical Course of Coronary Heart Disease Concomitant with Asthma

Abstract

The objective: to study features of the clinical course of coronary heart disease (CHD) concomitant with asthma (BA). **The materials and methods:** 180 patients were enrolled, 90 of them suffered from both CHD and BA (the first group), and 90 had CHD only (the second group). The examination included complaint collection, studying medical history, medical examination, percussion, auscultation, blood pressure (BP) measurement using Korotkoff method twice a day (in the morning and in the evening), heart rate (HR) measurement, 24-hour ECG monitoring, and echocardiography. Besides, standard biochemical analysis, including total cholesterol and low-density lipoprotein cholesterol, was performed. **The results.** The shortness of breath was the main complaint among 86 (95.5%) patients with both CHD and asthma; moreover, shortness of breath combined with palpitations in 73.8% of cases, and with angina pectoris only in 20% of cases. There was a significant difference between systolic and diastolic blood pressure; BP values were higher in CHD concomitant with asthma. The signs of left ventricular hypertrophy were revealed in the first group, these signs significantly differed from the ones in the second group. 24-hour ECG monitoring showed that myocardial ischemia was more frequent in the group, which consisted of patients with CHD. Besides, duration of ischemic depression per day was longer in this group. **The conclusion.** According to our findings, bronchial asthma occurs among patients with coronary heart disease in 16.6% of cases. A distinctive feature of bronchial asthma concomitant with coronary heart disease is that a patient often complaints to shortness of breath and palpitations, increase in blood pressure and heart rate, which indirectly indicates the activation of rennin-angiotensin-aldosterone and sympathoadrenal systems. It requires the inclusion of appropriate drug groups in the treatment of patients.

Key words: *coronary heart disease, bronchial asthma, comorbidity, 24-hour ECG monitoring*

Conflict of interests

The authors declare no conflict of interests.

Sources of funding

The authors declare no funding for this study.

Article received on 25.11.2019

Accepted for publication on 30.01.2020

For citation: Grigoryeva N. Yu., Ilyushina T. P., Kolosova K. S. et al. Clinical Course of Coronary Heart Disease Concomitant with Asthma. The Russian Archives of Internal Medicine. 2020; 10(2): 131-138. DOI: 10.20514/2226-6704-2020-10-2-131-138

24ECG — 24-hour ECG monitoring, AH — arterial hypertension, BA — bronchial asthma, BP — blood pressure, CHD — coronary heart disease, DBP — diastolic blood pressure, EchoCG — echocardiography, FC — functional class, HR — heart rate, PICS — post-infarction cardiosclerosis, RV — right ventricle, SBP — systolic blood pressure, SCHD — stable coronary heart disease.

*Contacts: Kseniya S. Kolosova, e-mail: ksunay@yandex.ru
ORCID ID: https://orcid.org/0000-0003-2586-0982

The study of various diseases in their combined course has been very relevant in the clinical treatment of internal diseases in recent years [1].

It is quite obvious that for the successful treatment of a comorbid patient, physicians should have an idea of the main reasons for the development of combined pathologies, which, according to some authors, can be divided into internal and external ones. Internal causes include similar etiopathogenesis of a number of diseases, one disease being a risk factor for another one, as well as widely discussed genetic disposition. Similar lifestyle and behavioral characteristics, the environment, the patient's microbiome, which is being actively investigated, and drug interactions should be classified as external causes.

Based World Health Organization (WHO) data on noncommunicable diseases of the 21st century, most deaths in economically developed countries will be associated primarily with cardiovascular diseases. However, it is also noted that the leading and competing reasons will include oncological diseases, pathologies associated with disorders of carbohydrate metabolism, and, of course, bronchopulmonary diseases [2, 3].

At present, the course of coronary heart disease (CHD) in patients with chronic obstructive pulmonary disease has been studied quite well [4, 5].

At the same time, there is evidence that the prevalence of CHD in patients with bronchial asthma (BA) is higher than in the general population. Therefore, it is of interest to study the characteristics of the course of coronary heart disease in patients with BA, as well as to find any common pathogenic mechanisms. Currently, patients with BA mainly use inhaled glucocorticoids, which excludes a distinct probability of atherosclerosis developing in the setting of BA, which can be associated with side effects of drugs [5]. Mechanisms of coronary heart disease developing in connection with BA are not well understood. CHD and BA that are developing in the same patient are likely to have pathogenic relations at a certain stage, although the relationship of these diseases at the level of risk factors is hardly in evidence. However, there is some evidence that BA and CHD have common development factors, as well as overlapping pathogenesis pathways [6-9].

Among the features of the clinical course of coronary heart disease in patients with BA, a significant number of atypical forms of myocardial infarction development [7, 10, 11], as well as of low-symptom and painless forms of chronic CHD (40.7-66.7% of cases) can be distinguished [11]. It is critically important that in up to 75% of cases, patients with BA die from CHD and not from complications of pulmonary disease [6-9]. Moreover, patients with BA may have no history of cardiovascular diseases, but an asymptomatic or atypical CHD is a common cause of sudden death [10, 11]. The definition of the following separate phenotype is justified: when bronchial asthma and cardiovascular diseases in one patient have characteristic features that have an effect on the development, prognosis and outcome of both diseases [5].

As early as the 1970s, scientists have proved the development of heart rhythm disorders in patients with chronic bronchopulmonary pathology. The most important factors that can cause arrhythmias related with BA include hypoxemia and related acid-alkaline and electrolyte imbalance, pulmonary hypertension and chronic cor pulmonale, as well as concomitant CHD [1, 10, 12].

Thus, the study of the course of coronary heart disease in patients with BA is important today.

In this regard, the **aim** of this research was to study the features of the clinical course of CHD concomitant with BA.

Materials and Methods

The study included the analysis of the outpatient medical records of patients who received treatment at local clinic No. 3 of the city of Arzamas in the Nizhny Novgorod Region and were diagnosed with CHD, namely stable coronary heart disease (SCHD) of functional class (FC) II and III. Out of 2,150 people who met the criteria for enrollment, 358 subjects, i. e. 16.6%, had bronchial asthma as a concomitant disease.

One hundred and eighty subjects underwent further analysis; 90 of them had a combination of CHD and BA (group 1), and the other 90 had CHD without BA (group 2). A retrospective study was conducted; patients were selected by free conversion

Table 1. *The distribution of patients by gender and age*

	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	P
Male, n (%)	33 (36)	38 (43)	0.8
Female, n (%)	57 (64)	52 (57)	0.6
Age, M±SD, y.o.	62.5±7.2	59.7±8.2	0.07

Note: CHD — coronary heart disease, BA — bronchial asthma

Table 2. *The characteristics of the studied groups*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)
CHD duration, years	7.2 [6.9; 8.1]	8.2 [8.0; 8.5]
BA duration, years	11.7 [9.2; 13.1]	-
History of smoking, n (%)	26 (28.8)	24 (26.6)
Functional class of CHD II FC, n (%)	25 (28.8)	29 (32.2)
III FC, n (%)	65 (72.2)	61 (68.8)
History of MI, n (%)	11 (12.2)	14 (15.5)
AH, st. I or II, n (%)	82 (91.1)	72 (80)
Functional class of CHF, n (%)		
I	22 (24.4)	18 (20)
II	68 (75.5)	72 (80)
DM, n (%)	18 (20)	16 (17.7)
Mild BA n (%)	24 (26.6)	-
Moderate BA, n (%)	66 (73.4)	-
BA combined, n (%)	90 (100)	-
RF, n (%)		
1st Degree	28 (31.1)	-
2nd Degree	62 (68.8)	-

Note: CHD — coronary heart disease, BA — bronchial asthma, SCHD — stable coronary heart disease, FC — functional class, MI — myocardial infarction, CHF — chronical heart failure, DM — diabetes mellitus, RF — respiratory failure

method, outpatient records of the patients of local clinic No. 3 were analyzed.

Table 1 shows the distribution of patients in groups by gender and age.-

Table 2 presents the characteristics of the patients.-

Concomitant pathology in the group of patients with CHD and BA was represented by arterial hypertension of stage 1-2 (82; 90%) and type II diabetes mellitus (18; 20%). In group 2, arterial hypertension of stage 1-2 (72; 80%) and type II diabetes mellitus (16; 17.7%) were also found.

There were no significant differences in the duration of CHD course in patients with BA. In the studied patients, CHD developed alongside existing BA.

All patients underwent general clinical examination that included data acquisition (complaints), studying case history, examination, percussion and auscultation, blood pressure (BP) measurement according to Korotkoff method twice a day in the morning and evening for one month, which was recorded by patients in an observation diary, heart rate (HR) measurement, 24-hour ECG monitoring (24ECG), transthoracic echocardiography (EchoCG). Standard blood biochemistry was also performed, with determination of total cholesterol and low-density lipoprotein cholesterol.

Patients were diagnosed with coronary heart disease based on anamnesis, clinical data, functional

diagnostic methods according to the Federal Clinical Recommendations (2016); diagnosis was confirmed with selective coronary angiography in 68% of patients. Patients were diagnosed with BA based on anamnesis, clinical data, and functional diagnostic methods in accordance with the Federal Clinical Recommendations for the Diagnosis and Treatment of Bronchial Asthma 2016; Clinical Recommendations 2019 were taken into account when analyzing the data [12]. To assess the severity of BA, the recommendations described in "Global Initiative for Asthma" International Program (GINA, 2018) [5] were used. In accordance with the recommendations for mild persistent BA, all patients received inhaled glucocorticoids, for moderate BA — combined therapy with beta2-agonist and inhaled glucocorticoid. All patients with CHD received antiplatelet agents and statins. As antianginal treatment, patients with CHD and BA received calcium antagonist verapamil. The average daily dose was 193.3 ± 10.2 mg per day. Verapamil was prescribed earlier as patients were prone to tachycardia. The drug does not cause bronchial obstructive syndrome, and CHF signs in patients with SCHD did not exceed stage I-IIA. Patients with no BA received a beta-blocker (bisoprolol). Patients with arterial hypertension also received thiazide diuretics and renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker).-

Statistical data processing was carried out using the following software packages: IBM SPSS Statistics 24 (IBM), STATISTICA 10.0 for Windows (StatSoft), and Microsoft Office Excel 2016 (Microsoft). Difference was considered statistically reliable at significance level $p<0.05$. The normality of the distribution of the analyzed characteristics was evaluated with the help of Scheffe's test, as well as on the basis of descriptive statistics analysis: coefficient of variation, average value and median, skewness and kurtosis normality test. Characteristics close to normal distribution were described by mean values, standard deviations (M±sd, where M is mean value, sd is standard deviation). Distributions of quantitative data, different from normal distribution, were described using median and interquartile range as 25% and 75% percentiles, i. e. the upper boundary of the 1st and lower boundary of the 4th quartile (Me [25p; 75p]). Qualitative data were summarized by calculating the proportion of observations (as percent) of a particular category in the study sample. The comparison of two samples in the analysis of variables measured using interval scales and having a normal distribution was carried out using parametric Student t-test for independent groups and non-parametric Mann-Whitney U test. To study the relationships between random variables, correlation analysis was used with the calculation of nonparametric Spearman correlation coefficient with obligatory visual control of scatterplots and removal of outliers. Difference was considered statistically reliable at significance level $p\leq0.05$. Values of p less than 0.001 were indicated as $p<0.001$. The study was carried out in accordance with Good Clinical Practice standards and principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee. Prior to enrollment, all participants gave their written informed consent.

Results and Discussion

It was found that the main complaint in the group of CHD with BA was shortness of breath — 86 (95.5%) patients; in 73.8% of cases shortness of breath was combined with palpitations, and only in 20% of cases — with chest pains. All patients complained of coughing. In the group of CHD without BA, patients most often complained of chest pains — 56 (50.4%), shortness of breath occurred in 51 (45.9%) patients.

Blood pressure in all patients included in the study was measured in the morning and in the evening, at the same time, for one month, on both hands, according to Korotkoff method. According to the analysis results in the group with CHD and BA, systolic blood pressure (SBP) in the daytime was 165.34 [112.4; 176.3] mm Hg ($p = 0.004$), diastolic blood pressure (DBP) was 95.21 [86.3; 102.1] mm Hg ($p = 0.001$). In the group with CHD and with no BA, SBP in the daytime was 155.3 [132.4; 173.6] mm Hg ($p = 0.003$), and DBP was 82.7 [74.3; 93.21] mm Hg ($p = 0.002$). In the evening, SBP in the group with CHD and BA was 160.7 [109.2; 169.1] mm Hg ($p = 0.002$), and DBP was 90.9 [82.7; 103.5] mm Hg ($p = 0.001$). In the

group with CHD and with no BA, SBP in the evening was on average 152.8 [129.9; 171.2] mm Hg (p = 0.012), and DBP was 78.4 [69.8; 91.31] mm Hg (p = 0.014). There was a significant difference in SBP and DBP between the groups in both morning and evening time (p<0.05).

Thus, despite the fact that there were no significant differences in the number of patients with AH between the groups, significantly higher blood pressure was observed in patients with BA and CHD. According to the literature, patients with BA and AH are characterized by poor adherence to treatment with antihypertensive drugs, as they focus on pulmonary disease [3]. In addition, the achievement of the target BP level in cases of BA is more difficult, since BA itself, especially its exacerbation, as well as drugs used for treatment, can contribute to arterial hypertension [3]. Steady rise in systemic blood pressure related to BA leads to postcapillary pulmonary hypertension, interstitial edema and pneumosclerosis with the formation of irreversible components of bronchial obstruction [6, 11]. There is evidence that BA can accelerate the rate of AH development, as well as the degree of left ventricular hypertrophy [6].

A comparative analysis of echocardiographic findings is shown in Table 3.

In the group with CHD and BA, signs of LV hypertrophy were found. Left ventricular myocardial mass index (LVMI) in women of the CHD+BA group was 142.7 ± 12.6 g/m2, of the CHD group — 118.3 ± 9.2 g/m2 (p = 0.024); in men of the CHD+BA group — 162.6 ± 7.4 g/m2, of the CHD group — 148.34 ± 11.1 g/m2 (p = 0.046). It can be assumed that not only cardiac, but also pulmonary pathology has an effect on the development of myocardial hypertrophy in patients with CHD combined with BA [11].

Table 3. *The EchoCG parameters in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	P
LV ESD, cm	4.1 [3.2; 4.1]	3.6 [2.9; 5.3]	p = 0.008
LV EDD, cm	5.6 [4.3; 6.8]	4.2 [2.7; 6.4]	p = 0.012
LV ESV, ml	63 [58.21; 67.3]	60 [53.31; 64.2]	p = 0.017
LV EDV, ml	121 [112; 139]	111 [103; 131]	p = 0.022
SV, ml	57 [54; 65]	52 [49; 59]	p = 0.023
EF, %	58 [53; 64]	61 [56; 70]	p = 0.008
LVPWd, cm	1.3 [1.1; 1.6]	1.0 [0.8; 1.3]	p = 0.003
IVSTd, cm	1.3 [1.1; 1.6]	1.1 [0.9; 1.4]	p = 0.004
LVM, g	251 [220; 312]	245 [220; 260]	p = 0.003
WMSI	1.2 [1.1; 1.3]	1.0 [1.0; 1.3]	p = 0.03
LA, cm	3.85 [3.7; 4.2]	3.67 [3.5; 4.3]	p = 0.006
E/A LV	0.62 [0.4; 0.8]	0.84 [0.4; 0.9]	p = 0.09
LVDF, ms	218 [120; 224]	215 [208; 225]	p = 0.02
RA, cm	3.7 [3.5; 4.2]	3.3 [3.0; 3.7]	p = 0.003
L RV, cm	6.68 [4.8; 8.0]	5.8 [3.7; 7.8]	p = 0.009
S RV, cm	4.6 [2.9; 6.8]	4.1 [3.3; 6.2]	p = 0.084
RVWT, cm	0.5 [0.5; 0.7]	0.4 [0.3; 0.5]	p = 0.003
mPAP, mm Hg	24.1 [19.4; 30.0]	20.3 [17.3; 27.6]	p = 0.001
E/A RV	0.47 [0.28; 0.74]	0.51 [0.42; 0.83]	p = 0.029

Note: CHD — coronary heart disease, BA — bronchial asthma, LV ESD — left ventricular end systolic dimension, LV EDD — left ventricular end diastolic dimension, LV ESV — left ventricular end systolic volume, LV EDV — left ventricular end diastolic volume, SV — stroke volume, EF — ejection fraction, LVPWd — left ventricular posterior wall thickness, IVSTd — interventricular septum thickness, LVM — left ventricular mass, WMSI — wall motion score index, LA — left atrium, E/A LV — peak early diastolic LV filling velocity / peak atrial filling velocity ratio, LVDF — left ventricular diastolic filling, RA — right atrium, L RV — right ventricle mid-diameter, S RV — right ventricle basal diameter, RV T — right ventricular wall thickness, mPAP — mean pulmonary arterial pressure, E/A RV — peak early diastolic RV filling velocity / peak atrial filling velocity ratio

The evaluation of right heart parameters is of great importance for patients with CHD and BA. A statistically significant difference in the size of right atrium (RA) was revealed in patients of the CHD+BA group compared with the group with CHD but without BA (p = 0.003). Dimensions of RA and right ventricle (RV) in both groups were within the normal range. This suggests that patients still have no dilatation and no right heart hypertrophy. This is probably because the study included patients with non-severe bronchial asthma, and there were no patients with fixed bronchial obstruction, which could lead to the development of chronic cor pulmonale.

According to 24ECG results, it was found that the number of myocardial ischemia episodes in the group with CHD but without BA was greater than in the CHD+BA group (p = 0.003) (Table 4).

The duration of ischemic depression per 24 hours in the group with CHD but without BA was also longer than in the CHD+BA group (p = 0.03).

According to A.L. Vertkin et al. (2015), episodes of myocardial ischemia are revealed in 0.5-1.9% of apparently healthy individuals. The interpretation of ischemia in patients with BA is complicated because degenerative myocardial changes related to pulmonary hypertension and hypoxemia can be found not only in the right but also in the left ventricle [1].

In the CHD+BA group, in comparison with the CHD group without BA, average daily HR was significantly higher (p = 0.008), as well as average HR during daytime (p = 0.004) and during nighttime (p = 0.007) (Table 5).

Increased heart rate in patients with BA is probably not associated with beta2-agonists, since most patients with BA (92%) received a combination drug with a selective beta2-agonist vilanterol, which has no adverse effect on cardiovascular system [13].

According to 24ECG results in the CHD+BA group, a greater number of extrasystoles of different types were recorded in comparison with the patients with CHD but without BA. However, there was no significant difference in the number of supraventricular extrasystoles (217.12 [212; 223] extrasystoles in the CHD+BA group; 205.08 [202; 208] extrasystoles in the CHD group, p = 0.07). Ventricular extrasystoles associated with CHD and BA were recorded statistically more frequently — 78.6 [68.9; 80.2] than related to CHD without BA — 58.4 [56.2; 62.2], p = 0.007. Results of 24ECG are comparable with patients' complaints of palpitations, which were more common in CHD with BA. One of the triggers of arrhythmias in patients with

Table 4. *The 24ECG parameters in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	p
The number of episodes of ischemic ST-segment depression/24 hours	5 [4.4; 5.2]	8 [4.9; 9.4]	0.003
The mean duration of ischemic ST-segment depression/24 hours, min	2.02 [1.02; 3.18]	5.06 [0.9; 7.0]	0.03
Maximal ST-segment depression, mm	1.59 [1.03; 1.9]	1.8 [1.04; 2.02]	0.03

Note: 24ECG — 24-hour ECG monitoring, CHD — coronary heart disease, BA — bronchial asthma

Table 5. *Heart rate values in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	p
Average daily HR, bpm	82.2 [80.5; 84.2]	73.6 [70; 78]	0.008
Average HR during daytime, bpm	78.4 [76.8; 80]	65.4 [62.4; 74.7]	0.004
Average HR during nighttime, bpm	74.6 [74.0; 78]	67.4 [64.2; 72.8]	0.007

Note: HR — heart rate, CHD — coronary heart disease, BA — bronchial asthma

CHD and BA is hypoxia and the intake of several bronchodilators, namely beta2-agonists, especially short-acting ones [11]. In addition, during this study, patients with CHD but without BA took beta-blockers that reduce ectopic myocardial activity [14].

The study of lipid metabolism revealed that in patients with CHD combined with BA, higher total cholesterol (TC) was observed in comparison with the CHD group without BA (5.8 ± 0.13 mmol/L and 5.2 ± 0.24 mmol/L, p = 0.013). The level of triglycerides (TG) in the CHD+BA group was 1.4 ± 0.04 mmol/L, and in the CHD group without BA — 1.4 ± 0.06 (p = 0.022). Low-density lipoprotein cholesterol (LDL-C) in group 1 was 1.4 ± 0.01 mmol/L, and in group 2 — 0.99 ± 0.03 mmol/L (p = 0.014); high-density lipoprotein cholesterol (HDL-C) in the CHD+BA group was 0.7 ± 0.04 mmol/L, and in the CHD group without BA — 0.9 ± 0.06 (p = 0.034). Patients with BA were characterized by poor adherence to lipid-lowering treatment, as they focus on pulmonary disease. According to the literature, a more aggressive course of atherosclerosis is discussed in presence of BA due to the prolonged circulation of pro-inflammatory cytokines in the blood which induce inflammatory process in plaques, their growth and damage [3].

Conclusion

According to this study, BA occurs in patients with CHD in 16.6% of cases. According to the literature, the incidence of CHD combined with BA is 6.8-34.3% [1].

Our study allowed finding a number of characteristic features of the course of CHD in patients with BA. First, patients quite often complain of shortness of breath and palpitations and rarely of typical angina pain. This is because shortness of breath related to CHD and BA will prevail in the clinical evidence and will be of mixed nature. A physician should figure out the leading cause of dyspnea — whether it is cardiac or pulmonary. This is necessary for the choice of drug therapy. It is impossible to answer this question during routine examination. A number of diagnostic tests are required, in particular a cardiopulmonary stress test, which is very informative and safe for this category of patients.

Secondly, patients with CHD and BA have increased BP and HR, which indirectly indicates the activation of renin-angiotensin-aldosterone and sympathoadrenal systems and requires appropriate groups of drugs in the treatment of such patients. Objective hypersympathicotonia related to BA is also confirmed by the results of 24ECG, which reveal different types of arrhythmias in patients; they may be caused by the state of chronic hypoxia, or by certain medications for the treatment of BA itself. In our opinion, studying the possibility of using highly selective beta blockers for concomitant BA is very promising.

Thus, the issues of pathogenic mechanisms, clinical and functional features of the course of CHD concomitant with BA, and the choice of optimal treatment for this category of patients require further study, and we will continue this study in future.

Author Contribution:

N. Yu. Grigoryeva (ORCID ID: https://orcid.org/0000-0001-6795-7884),
T. P. Ilyushina (ORCID ID: https://orcid.org/0000-0001-5756-6054),
K. S. Kolosova (ORCID ID: https://orcid.org/0000-0003-2586-0982),
N. B. Koroleva (ORCID ID: https://orcid.org/0000-0001-9993-4812),
A. A. Streltsova (ORCID ID: https://orcid.org/0000-0001-9016-3011),
D. V. Solovyeva (ORCID ID: https://orcid.org/0000-0003-0254-7192): concept and design of the research, material collection and processing
N. Yu. Grigoryeva (ORCID ID: https://orcid.org/0000-0001-6795-7884),
T. P. Ilyushina (ORCID ID: https://orcid.org/0000-0001-5756-6054): substantiation and writing of the work, editing, approval for publication

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