INITIAL ADMINISTRATION OF β_2-AGONISTS REDUCES THE RISK OF BRONCHOSPASM CAUSED BY β_1-BLOCKERS IN COMORBID CARDIORESPIRATORY PATHOLOGY

Smolyakova EV[1,2] ✉, Sinitsyn EA[2], Zykov KA[1,2]

[1] Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia

[2] Pulmonology Research Institute of Federal Medical Biological Agency, Moscow, Russia

In the treatment of patients with cardiorespiratory pathology, it is often necessary to simultaneously administer drugs that affect β-adrenergic receptors: β_1-adrenoblockers and β_2-agonists. β_1-blockers can trigger a bronchospasm in patients with bronchoobstructive diseases, therefore, practitioners often decide not to prescribe them. This work aimed to evaluate functional parameters of patients with cardiovascular and bronchoobstructive diseases in the context of different sequences of administration of selective β_1-blockers (bisoprolol) and long-acting β_2-agonists (formoterol). This prospective, single-center 2-week pilot study involved 30 individuals suffering the aforementioned diseases. Using the envelopes method, we divided the patients into two groups of 15 people each. First group started therapy with a long-acting β_2-agonist, second group — with a selective β_1-adrenoblocker. While taking the β_1-adrenoblocker, patients underwent a four-hour spirometric test enabling assessment of the external respiration function parameters. The tests and assessments have shown that the value of FEV1 went down in 33.3% of those who started therapy with a selective β_1-adrenoblocker (bisoprolol 2.5 mg), and in the group that first took a long-acting β_2-agonist for a week and then added bisoprolol 2.5 mg to the regimen the said value dropped in 7% of patients only. Thus, preceding long-acting β_2-agonists, formoterol in particular, reduced the risk of bronchospastic incidents triggered by selective β_1-adrenoblocker (bisoprolol) in patients with cardiorespiratory pathology.

Keywords: cardiovascular diseases, bronchoobstructive diseases, cardiorespiratory pathology, β_1-adrenoblockers, β_2-agonists

Author contribution: Smolyakova EV — recruitment of patients, processing of the results, article authoring; Sinitsyn EA — discussion of the results; Zykov KA — patient treatment management, discussion of the study results, article authoring.

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✉ **Correspondence should be addressed:** Ekaterina V. Smolyakova
Orekhovy bulvar, 28, 115682, Moscow, Russia; smolyakovak@mail.ru

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ПРИ КОМОРБИДНОЙ КАРДИОРЕСПИРАТОРНОЙ ПАТОЛОГИИ ИНИЦИАЛЬНОЕ НАЗНАЧЕНИЕ β_2-АГОНИСТОВ СНИЖАЕТ РИСК БРОНХОСПАЗМА, ВЫЗВАННОГО β_1-АДРЕНОБЛОКАТОРАМИ

Е. В. Смолякова[1,2] ✉, Е. А. Синицын[2], К. А. Зыков[1,2]

[1] Московский государственный медико-стоматологический университет имени А. И. Евдокимова, Москва, Россия

[2] Научно-исследовательский институт пульмонологии Федерального медико-биологического агентства, Москва, Россия

При лечении пациентов с кардиореспираторной патологией часто необходимо одновременное использование препаратов, воздействующих на β-адренорецепторы: β_1-адреноблокаторы и β_2-агонисты. Из-за возможности развития бронхоспазма у пациентов с бронхообструктивными заболеваниями на фоне использования β_1-адреноблокаторов, практикующие врачи нередко отказываются от их назначения. Целью работы было оценить функциональные параметры у пациентов с сердечно-сосудистыми и бронхообструктивными заболеваниями при различной последовательности назначения селективных β_1-адреноблокаторов (бисопролола) и β_2-агонистов длительного действия (формотерола). В пилотное одноцентровое проспективное исследование было включено 30 пациентов с сердечно-сосудистыми заболеваниями и бронхообструктивными заболеваниями, длительность исследования составила 2 недели. Пациенты методом «конвертов» были разделены на две группы по 15 человек. Первая группа пациентов начинала старт терапии с приема β_2-агониста длительного действия, а вторая группа — с приема селективного β_1-адреноблокатора. На фоне приема β_1-адреноблокатора пациентам проводили четырехчасовую спирометрическую пробу с оценкой параметров функции внешнего дыхания. Показано, что у начинающих старт терапии с приема селективного β_1-адреноблокатора (бисопролола 2,5 мг) снижение ОФВ1 происходило у 33,3% человек, в то время как у принимающих бисопролол 2,5 мг на фоне недельного приема β_2-агониста длительного действия процент выявленных случаев снижения ОФВ1 составил всего 7%.Таким образом, предварительное назначение β_2-агонистов длительного действия, в частности формотерола, снижало риск бронхоспастического действия селективного β_1-адреноблокатора — бисопролола у пациентов с кардиореспираторной патологией.

Ключевые слова: сердечно-сосудистые заболевания, бронхообструктивные заболевания, кардиореспираторная патология, β_1-адреноблокаторы, β_2-агонисты

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✉ **Для корреспонденции:** Екатерина Владимировна Смолякова
Ореховый бульвар, д. 28, 115682, г. Москва, Россия; smolyakovak@mail.ru

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Cardiovascular and bronchoobstructive diseases, namely bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD), are among the main public health problems in people aged 40 and older [1]. The reasons behind the high prevalence of comorbidity of cardiovascular and bronchoobstructive pathologies are the common risk factors, pathophysiological processes that jointly aggravate the course of the diseases [2, 3]. From the epidemiological point of view,

cardiovascular diseases (CVD) are among the top reasons of death of patients with COPD and BA [4]. The drugs used to treat a cardiorespiratory pathology are β_1-blockers and β_2-agonists, which block or activate the adrenergic system. These drugs are not 100% selective, and the receptors are located close to each other; these factors translate into a possibility of cross-receptor interaction, which often leads to side effects and to suboptimal effect of the drugs on both conditions: underprescription or rejection of pathognomonic therapy [5].

β_1-Blockers are widely used in the treatment of CVD, the particular conditions being coronary heart disease, cardiac arrhythmia and heart failure [6]. There are two types of β-blockers: non-selective, which block both β_1- and β_2-adrenergic receptors, and selective (cardioselective) β_1-adrenoblockers, which act mainly on β_1-adrenergic receptors. Traditionally, there are concerns about prescribing β-blockers to patients with concomitant COPD and BA, since they can cause reduction of the vital lung capacity, bronchospasm, erosion of the efficacy of short-acting β_2-agonists taken to arrest an attack, same as erosion of the efficacy of long-acting β_2-agonists, which is the result of direct blockade of β_2-adrenergic receptors of bronchi's smooth muscles. Therefore, the preferred drugs should be cardioselective β_1-adrenoblockers [7, 8]. At that, it should be remembered that selectivity of β_1-blockers deteriorates as their dose grows up [9]. Even nebivolol, the selectivity of which is 1:22–46, does not eliminate the risks of bronchospasm because of uneven distribution of β-adrenergic receptors through organs and tissues.

In turn, β_2-agonists are the main symptomatic drugs for patients with a bronchoobstructive pathology. However, since there are β_2-adrenoreceptors in the heart, such drugs, especially their short-acting varieties, can indirectly (through activation of the sympathoadrenal system) provoke growth of blood pressure and heart rate in patients with comorbid CVDs, and, according to some authors, decrease of the concentration of potassium in the blood triggered by higher doses of β_2-agonists may be the cause of development of life-threatening arrhythmias [10].

At the same time, combined intake of selective β_1-adrenoblockers and β_2-agonists, through suppression of tachycardia and hypertension associated with high doses of β_2-agonists taken to arrest COPD and BA exacerbations, has shown capability to decrease the frequency of cardiovascular events. Some randomized trials, as well as a number of meta-analyses, have revealed a decreased CVD-associated mortality among COPD and BA patients taking β_1-adrenoblockers [11, 12]. There is also evidence suggesting that β_2-agonists can mitigate the risk of cardiovascular complications through reduction of the residual volume of air in the lungs, which translates into lighter inspiratory dyspnea [13]. Moreover, the right ventricular compliance indicators improve [13], and the pulmonary artery pressure goes down [14], which means fewer COPD and BA exacerbations raising the risk of cardiovascular diseases and mortality.

Thus, treatment of patients with a combined cardiorespiratory pathology often requires simultaneous administration of a selective β_1-adrenoblocker and a β_2-agonist. Today, medical professionals seek practical recommendations covering the order of prescription of these drugs if they need to be used together. It should be noted that currently, there are no evidence-based data on the comparative safety and efficacy of prescribing β-agonists first and β-adrenoblockers second in a regimen, nor is there evidence describing the approach involving initial prescription of β-adrenoblockers. This study aimed to determine the preferred sequence of administration of selective β_1-adrenoblockers (bisoprolol) and long-acting β_2-agonists (formoterol) in patients with cardiovascular and bronchoobstructive diseases based on the assessment of functional parameters.

METHODS

This work was a was pilot, single-center prospective study that involved 30 patients (66.97 ± 9.84 years, 18 male, 12 female). The inclusion criteria were: cardiovascular diseases — arterial

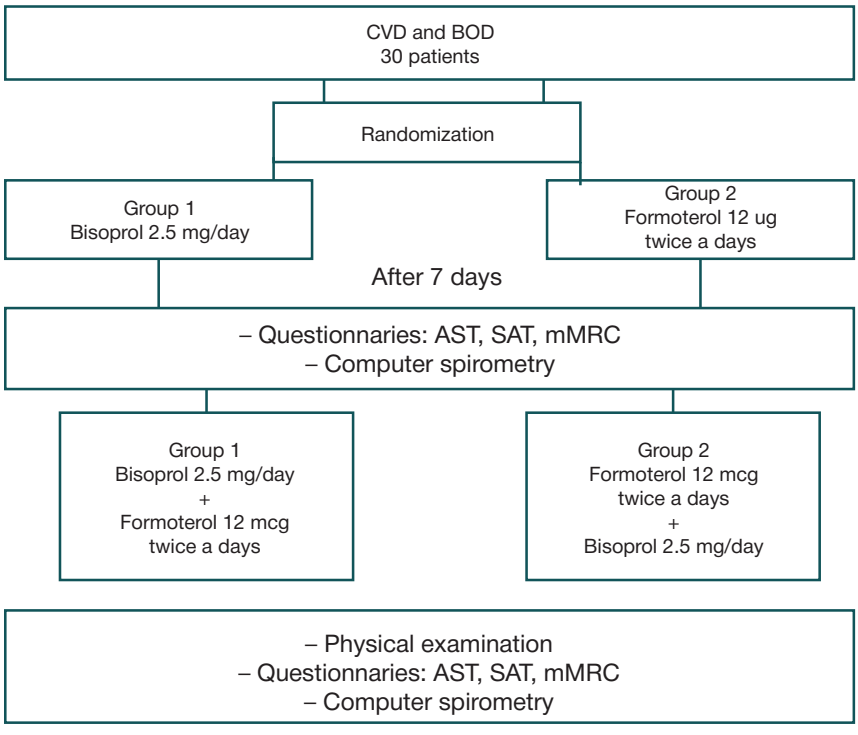

Fig. 1. Study design. BP — blood pressure; AST — Asthma Control Test; BOD — bronchoobstructive diseases; CAT — COPD Assessment Test, mMRC — modified Medical Research Council Dyspnea Scale

Table 1. Clinical characteristics of the patients with CVD and BOD, groups 1 and 2 (medical history data)

Patient characteristic	Patients with CVD and BOD (*n* = 15), group 1	Patients with CVD and BOD (*n* = 15), group 2
Age, years	65.9 ± 10	68 ± 10.3
Gender, male/female, %	46.7 / 53.3	73.5 / 26.5
AH, degrees I, II, III, %	0; 46.7; 53.3	0; 40%; 60.2.
CHD functional class, I, II, III, %	6.6; 40; 0	26.7; 13.3; 20
PICS, %	26.7	40
HA, %	46.7	26.7
BA, %	26.7	20
COPD, %	53.3	66.7
COPD + BS, %	20	13.3
ACT, points	17.00 [15.50; 20.00]	17.00 [13.00;18.00]
CAT, points	16.00 [14.00; 24.00]	22.00 [21.00; 25.00]
mMRC, points	2 [1.50; 3.00]	3.00 [2.00; 3.00]
CCA therapy, %	40	53.3
ACE inhibitors therapy, %	13.3	26.7
ARB therapy, %	73.5	60.2

Note: the data are given as M ± SD and % of the total number of patients; * — $p < 0.05$; AH – arterial hypertension; ACT — asthma control test; BA — bronchial asthma; CCA — calcium channel antagonists; ARB — angiotensin-2 receptor blockers; CHD — coronary heart disease; ACE inhibitors — angiotensin converting enzyme inhibitors; mMRC — modified medical research council dyspnea scale; HA — heart arrhythmia; PICS — post-infarction cardiosclerosis; CAT — COPD assessment test; COPD — chronic obstructive pulmonary disease.

hypertension, coronary heart disease, cardiac arrhythmia, — concomitant with bronchoobstructive diseases (BOD) — bronchial asthma, chronic obstructive pulmonary disease. All the patients were prescribed a selective β_1-adrenoblocker (bisoprolol) and a β_2-agonist (formoterol).

Using the envelopes method, we divided the patients into two groups comparable in age, gender, and therapy at the time of inclusion in the study. Tables 1 and 2 present clinical characteristics of the patients [15].

Patients of group 1 started therapy with a β_1-adrenoblocker, bisoprolol 2.5 mg, and for group 2, the initial drug was a long-acting β_2-agonist, formoterol 12 μg twice a day. A week later, group 1 began taking formoterol, group 2 — bisoprolol. Selection of the initial doses of the drugs was based on the preceding computer spirometry, specialized tests and questionnaires (Fig. 1). SuperSpiro spirometer enabled spirometry (MICRO MEDICAL; UK), and the acquired values were compared to the spirometry reference values developed by the European Coal and Steel Community (ECSC) in 1993.

In order to prevent the development of bronchospasm, all patients underwent a 4-hour spirometry before being prescribed the first dose of the β_1-adrenoblocker. This test allows evaluating the initial external respiration parameters (FVC — forced vital capacity, FEV1 — forced exhale volume in 1 s, FEV1/FVC) before taking the drug and 30 minutes, 90 minutes, 150 minutes and 240 minutes after taking bisoprolol 2.5 mg.

Participants of the study

A total of 30 patients (66.97 ± 9.84 years old, 18 male and 12 female) participated in the study. They were divided into two comparable groups of 15 people.

The inclusion criteria were: CVD and BOD, compensation stage, lack of any acute process at the time of screening for the study; confirmed BA diagnosed in accordance with the generally accepted clinical, laboratory and functional criteria (GINA 2017 [16]); COPD diagnosed in accordance with the GOLD 2017 criteria [17]; signature under the informed consent form confirming voluntary participation in the study.

The exclusion criteria were: severe CVD (acute cerebrovascular accident, myocardial infarction less than 6 months before inclusion in the study, unstable angina pectoris); exacerbation of COPD, BA less than 1 month before

Table 2. Clinical characteristics of the patients with CVD and BOD, groups 1 and 2 (laboratory and instrumental study data)

Patient characteristics	Patients with CVD and BOD (*n* = 15), group 1	Patients with CVD and BOD (*n* = 15), group 2
ECP, μg/l	21.9 ± 12.1	18.8 ± 15.2
CRP, mg/l	18.8 ± 15.2	5. 91 ± 7.5
ESR, mm/h	12.9 ± 10.8	13.7 ± 13.5
Leukocytes, 10^9/l	8.2 ± 1.8	7.9 ± 1.4
Erythrocytes, 10^9/l	5.2 ± 0.9	4.9 ± 0.4
Eosinophils, %	2.88 ± 2.07	3.99 ± 2.2
SBP/DBP, mmHg	128.8/79.8 ± 11/3.8	126.7/78 ± 8.8/5.5
HR, beats/min	70.9 ± 9	68.9 ± 10.1
FEV1, % of the reference value	73.2 ± 11.7	78.86 ± 17.3
FVC, % of the reference value	95.8 ± 19.6	96.7 ± 17.9

Note: the data are given as M ± SD; * — $p < 0.05$; DBP — diastolic blood pressure; FEV1 — forced expiratory volume, 1 s; SBP — systolic blood pressure; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; ECP — eosinophilic cationic protein; FVC — forced vital capacity; HR — heart rate.

inclusion in the study; contraindications to intake of selective β_1-adrenoblockers and β_2-agonists; oncological diseases; pregnancy, breastfeeding; clinical conditions that, according to the doctor, prevent participation in the study.

The study was conducted at the National Medical Research Centre of Cardiology named after Academician E.I. Chazov, in the department of hypertension. The length of the study was 2 weeks, its key outcome — evaluation of functional parameters of patients with comorbidities in the context of different sequences of administration of selective β_1-adrenoblockers and long-acting β_2-agonists.

Statistical analysis

This was a pilot study, therefore, we did estimate power of the sample. PSPP 1.2.0 (GNY project; USA) enabled statistical processing of the data, and Kolmogorov–Smirnov test — verification of the distribution hypotheses. For quantitative variables in the context of normal distribution, we used the mean ± standard deviation, and for nonparametric indicators — median and percentiles [25; 75]. The differences were considered significant at $p < 0.05$.

RESULTS

Four-hour spirometry revealed no significant (over 20% from the baseline) drop of the level of FVC and FEV1; overall, the participants in both groups reported no deterioration of condition, which was subjectively assessed with the help of ACT, CAT, mMRC questionnaires (Table 3). However, analysis of data of all patients has shown that in 29 patient out of 30, bisoprolol 2.5 mg/day triggered a reversible decrease of FEV1, maximum to 300 ml, which is down 17% from the baseline, the recovery to which occurred after a bronchodilation test with salbutamol 400 mg (Figure 2). In most cases, FEV1 drops (in absolute values and in % from the baseline) were registered 30 minutes and 240 minutes after initial administration of bisoprolol 2.5 mg. We included the drop values starting from 2% (Fig. 2) into the calculations, thus eliminating the possibility of measurement error.

Statistical processing of the patient data by groups revealed a greater percentage of FEV1 reduction cases in group 1 (33.3% of the participants), where the therapy began with a selective β_1-adrenoblocker (bisoprolol 2.5 mg). At the same time, in group 2, which received a long-acting β_2-agonist (formoterol 24 μg) as the initial drug and started taking bisoprolol 2.5 mg only after 7 days of bronchodilation therapy, the share of those whose FEV1 decreased was 7% (Fig. 3).

DISCUSSION

The problems of drug therapy aimed at combined cardiovascular and bronchopulmonary pathologies, COPD and BA in particular, remain relevant. The need for β_1-adrenoblockers in treatment of patients with bronchoobstructive diseases remains a debatable subject. A meta-analysis of observational studies that included 15 cohort studies with a follow-up period of up to 7.2 years, all of which investigated the use of β_1-adrenblockers in patients with CVD and BOD, has shown that these drugs significantly reduce mortality and exacerbations of BOD [18]. The results of this analysis is confirmed in two other major studies. One of them demonstrated that cardioselective β_1-adrenoblockers boost the response to β_2-agonists and cause no clinically significant side effects on the part of the respiratory system [7]; another reported that administration of β_1-adrenoblockers decreases overall mortality and sudden cardiac death by reducing heart rate and prolonging the diastolic period of the cardiac cycle, which improves myocardial perfusion [19]. Still, there are registered cases of decreasing vital lung capacity in the context of regimens that start the therapy with β_1-adrenoblockers. Our study confirms that: against the background of complete clinical well-being and lack of any deterioration of condition, as reported by the patients with CVD and BOD comorbidities, FEV1 reversibly dropped, in the extreme case — to 300 ml and 7% of the baseline. In an earlier paper, 4-hour spirometry has also revealed decreasing FEV1 in patients with cardiorespiratory pathology, and the share of those in whom the drop exceeded 20% from the baseline was 6.4%. However, authors of that work emphasized that long-term use of selective β_1-adrenoblockers (bisoprolol) did not translate into a significant FEV1 and FVC decrease that could be detected by spirometry [20].

Taking into account the results of our study, patients at high risk of bronchospasm who require prescription of a β_1-adrenoblocker can be recommended a 4-hour spirometry in a hospital setting. The test will help practitioners initiate administration of β-adrenoblockers, starting with small doses and continuing with their gradual titration.

Our study lacked statistical power to allow an unambiguous conclusion, yet, we demonstrated that it is advantageous to start therapy with a long-acting β_2-agonist, thus reducing the risk of a bronchospastic component in patients with CVD and BOD comorbidities that need constant and long-term administration of β_1-adrenoblockers. Of course, this suggestion should be backed with more extensive clinical studies, which would seek to ultimately determine the variability of FEV1 against the background of different tactics of simultaneous administration of selective β_1-adrenoblockers and β_2-agonists.

Study limitations

The limitation of this study is the small sample of patients. However, the results are significant, which raises the need for continued research of this subject matter with sufficient statistical power.

Table 3. Dynamics of indicators as registered with CAT, ACT, MRC questionnaires, patients with CVD and BOD comorbidities, both groups

	CVD and BOD, group 1		CVD and BOD, group 2	
	baseline	a week later	baseline	a week later
ACT, points	17 [15.50; 20.00]	20 [19.00; 23.00]	17.00 [13.00; 18.00]	19.00 [17.00; 21.00]*
CAT, points	16 [14.00; 24.00]	13 [9.00; 15.00]	22.00 [21.00; 25.00]	17.00 [14.50; 21.50]*
mMRC, points	2 [1.50; 3.00]	1 [1.00; 2.00]	3.00 [2.00; 3.00]	2.00 [1.00; 2.50]*

Note: * — $p < 0.05$.

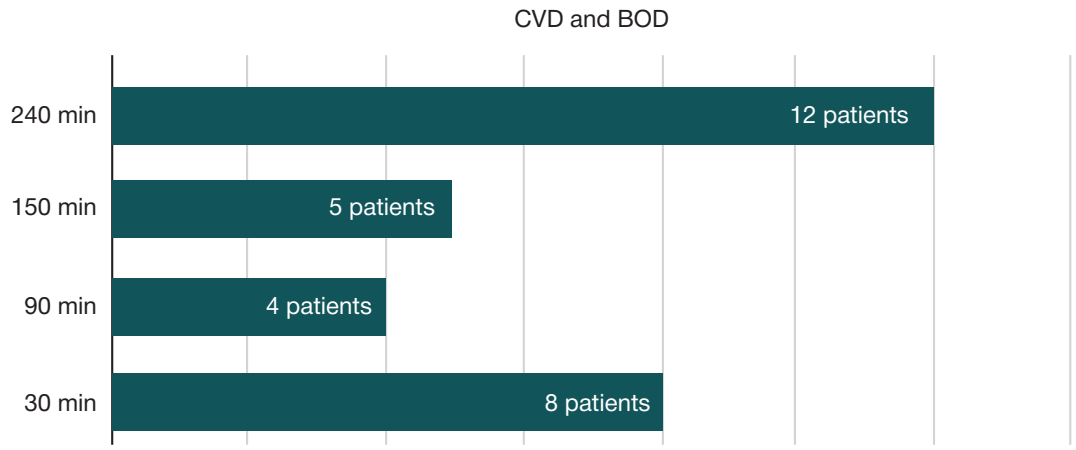

Fig. 2. Distribution of patients with the greatest FEV1 drop (in % from the reference values) at different time, CVD and BOD groups

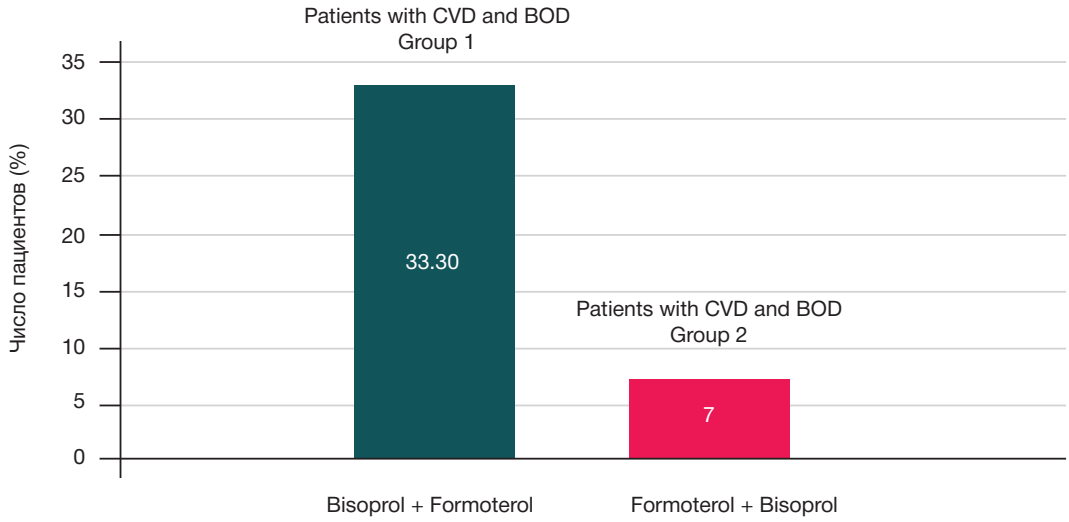

Fig. 3. Percentage of patients with CVD and BOD whose FEV1 decreased over 2% from the reference values

CONCLUSIONS

Despite the close pathogenetic relationships between CVD and BOD and availability of clinical recommendations covering these comorbidities, in everyday practice, medical professionals still face difficulties in selecting therapy for such patients. Our study has shown the importance of sequence in regimens involving both β_2-agonists and β_1-adrenoblockers. Starting the therapy with long-acting β_2-agonists, in particular formoterol, reduces the risk of bronchospastic effect of selective β_1-adrenoblocker, bisoprolol, in patients with a cardiorespiratory pathology. This phenomenon deserves attention and requires further studies on a larger sample of patients.

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