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Research Article

Influence of beta-blockers on mechanical dyssynchrony and cardiac remodeling in patients with ischemic chronic heart failure in the setting of revascularization

Irina V. Askari[1], Olga A. Osipova[1]

1 *Belgorod State National Research University, 85 Pobedy St. Belgorod 308015, Russian Federation*

Corresponding author: *Irina V. Askari* (askari.irina@mail.ru)

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Abstract

Introduction: Diastolic dysfunction (DD) and cardiac dyssynchrony (DS) are involved in the progression of chronic heart failure (CHF). A comparative analysis was conducted of the effect of a 6-month course of nebivolol and bisoprolol on DD, DS and metalloproteinase-9 (MMP-9) level in patients with ischemic chronic heart failure with preserved ejection fraction (HFpEF) and with midrange ejection fraction (HFmrEF), as well as in patients with comorbid type 2 diabetes mellitus (T2DM) in the setting of coronary artery bypass grafting (CABG) after 6 months of therapy.

Materials and methods: The study included 308 patients with CHF FC I-II, left ventricular ejection fraction (LVEF) >40%, who had undergone CABG. The average dose of nebivolol in patients with DS 6 months later was 5.1±2.6 mg/day, and bisoprolol – 4.9±2.4 mg/day. Echocardiography (EchoCG) and evaluation of MMP-9 in blood plasma were performed. Mechanical myocardial asynchrony was determined by calculating the standard deviation of time to peak systolic myocardial velocity (TS-SD) and maximum segment delay (TS12) using a 6-basal and-midsegment model.

Results and discussion: MMP-9 level in patients with CHF before CABG was 4.7 times higher ($p<0.001$). MMP-9 correlated with LVEF ($r=-0.60$, $p<0.001$), E/A ($r=-0.49$, $p<0.001$), DT ($r=0.43$, $p<0.001$), E` ($r=-0.58$, $p<0.001$) and DS: TS12 ($r=0.54$, $p<0.001$), TS-SD ($r=0.49$, $p<0.001$). The six-month course of nebivolol improved the values of DS: TS12 – by 30% ($p<0.001$), TS-SD – by 32% ($p<0.01$) and reduced the MMP-9 level by 11% ($p<0.001$). In patients with HFmrEF without DS nebivolol increased E/A by 19% ($p<0.01$), E` – by 16% ($P<0.05$), and decreased E/E' by 9% ($p<0.05$), DT – by 12% ($p<0.05$). In patients with HFpEF and DM2, nebivolol reduced TS12 by 37% ($p<0.01$), TS-SD – by 29% ($p<0.05$) and MMP-9 – by 13% ($p<0.05$).

Conclusion: The positive effect of nebivolol on the DS, DD of the LV in patients with HFpEF, HFmrEF and with comorbid type 2 diabetes mellitus. The six-month course of nebivolol decreased the MMP-9 level in patients with ischemic CHF after CABG, including patients with T2DM.

Keywords

chronic heart failure, coronary heart disease, dyssynchrony, diastolic function, coronary artery bypass grafting, metalloproteinase-9.

Introduction

Chronic heart failure continues to be one of the most common severe cardiovascular diseases with unfavorable prognosis (Fomin 2016, Mareev et al. 2017). It is generally accepted that CHF and its severity correlate with a decreased systolic LV function, which is estimated by the value of the left ventricular ejection fraction (LVEF). CHF with reduced ejection fraction (HFrEF) is diagnosed when left ventricle myocardial contractility is less than 40%. The most common CHF forms are HFpEF with LVEF over 50% and HFmrEF with LVEF from 40 to 49% (Rich et al. 2018). In recent years, much attention has been paid to studying HFmrEF, as its pathophysiology is poorly understood and its optimal treatment remains largely undetermined (Mohammed et al. 2012, Paulus and Tschöpe 2013, Upadhya et al. 2015).

Over the last decade, there have been active studies on the participation of LV diastolic dysfunction and DS in the progression of the heart failure (De Sutter et al. 2005, Lee et al. 2009). Ischemia and progressive interstitial fibrosis are assumed to be their development basis (Mohammed et al. 2015, Crendal et al. 2014). One of the potential biomarkers of cardiac fibrosis is MMP-9 (Querejeta et al. 2004, Zile et al. 2015). Its significant expression is associated with coronary arteritis (Choudhary et al. 2006, Tanindi et al. 2011), metabolic imbalance of extracellular matrix collagen and myocardial dysfunction (Gandhi et al. 2011). In this regard, the possibility of potency assay of MMP-9 to assess the antifibrotic activity of pharmacotherapy in patients with CHF of ischemic origin with preserved and midrange ejection fraction in the setting of revascularization is very promising and relevant.

Beta-blockers (β-blockers) are recommended as first-line therapy (Osipova 2013, Belsey et al. 2015) in patients with CHF and coronary heart disease (CHD). However, the choice of drugs from the group of β-blockers in patients with myocardial dissynchrony and ischemic HFpEF or HFmrEF in the setting of revascularization remains an open question.

In recent years, the number of patients with T2DM has been rapidly increasing. T2DM is considered as an independent risk factor for CHD and CHF progression (Radchenko and Koroliuk 2015, Dedov et al. 2015). In this regard, it is important to study the pleiotropic effects of nebivolol and bisoprolol on mechanical dissynchrony and collagen metabolism in patients with ischemic HFpEF or HFmrEF in the setting of the coronary revascularization and comorbid T2DM.

Objective of the study

To conduct a comparative analysis of the effect of long-term pharmacotherapy with β-blockers (nebivolol and bisoprolol) on structural and functional remodeling, mechanical dissynchrony of the myocardium and the level of MMP-9 in patients with ischemic HFpEF or HFmrEF in the setting of myocardial revascularization via CABG.

Materials and methods

The study included 308 patients aged 52 to 72 years (mean age 62±6 years) who were treated in the Cardiac Surgery Department of St. Ioasaph Belgorod Regional Clinical Hospital in the period from 2015 to 2018.

Entry criteria: 1) CHF FC I-II caused by coronary artery disease, obliterating atherosclerosis of coronary arteries and myocardial revascularization performed via CABG; 2) LVEF>40%; 3) Compensated type 2 diabetes mellitus on the background of concomitant antihyperglycemic therapy; 4) Patient Informed Consent to participate in the study.

Exclusion criteria: CHF FC III-IV; LVEF<40%; congenital heart disorders and acquired valvular heart diseases; myocarditis, pericarditis, cardiomyopathy, acute myocardial infarction; complicated postoperative period; comorbid acute inflammatory, infectious, oncologic, immune complex diseases; stable intraventricular conduction abnormalities; acute renal failure and chronic kidney disease (plasma creatinine >2.5 mg/dL); and dissent of the patient.

The general group (308 patients with ischemic CHF FC I-II) consisted of 258 (83.8%) men and 50 (16.2 %) women aged 52 to 72 years (mean age 62±6 years). Table 1 presents the characteristics of patients included in the study.

Patients were divided into 3 groups by the stratification randomization method. The clinical characteristics of the examined groups of patients are presented in Table 2. Group 1 consisted of 120 patients with ischemic CHF and EchoCG-confirmed mechanical DS; group 2 consisted of 120 patients with ischemic CHF without mechanical DS; group 3 consisted of patients with ischemic CHF, DS and comorbid T2DM. The study design is shown in Figure 1. All groups were further divided into subgroups according to the drug therapy with β-blocker (nebivolol and bisoprolol) using the random number table generated in STATISTICA. The study additionally evaluated a per-

Table 1. Clinical characteristic of the examined patients

Criteria	Value
Total number of the examined patients, n (%)	308 (100%)
Men, n (%)	258 (83.8%)
Women, n (%)	50 (16%)
Age, years	From 52 to 72
Meanage, years	62±6
CHF FC I, n (%)	159 (51.6%)
CHF FC II, n (%)	149 (48%)
LVEF 40–49 % n, (%)	109 (35.5%)
LVEF >50 %, n (%)	199 (64.5%)
QRS msec >120 msec, n (%)	58 (18.82%)
Previous myocardial infarction, n (%)	252 (82%)
Heart rhythm disorder, n (%)	77 (25%)
Ischemic mitral insufficiency up to degree 2, n (%)	107 (34.8%)
Type 2 diabetes mellitus, n (%)	68 (22%)

Note: CHF - chronic heart failure, FC - functional class, LVEF - left ventricular ejection fraction.

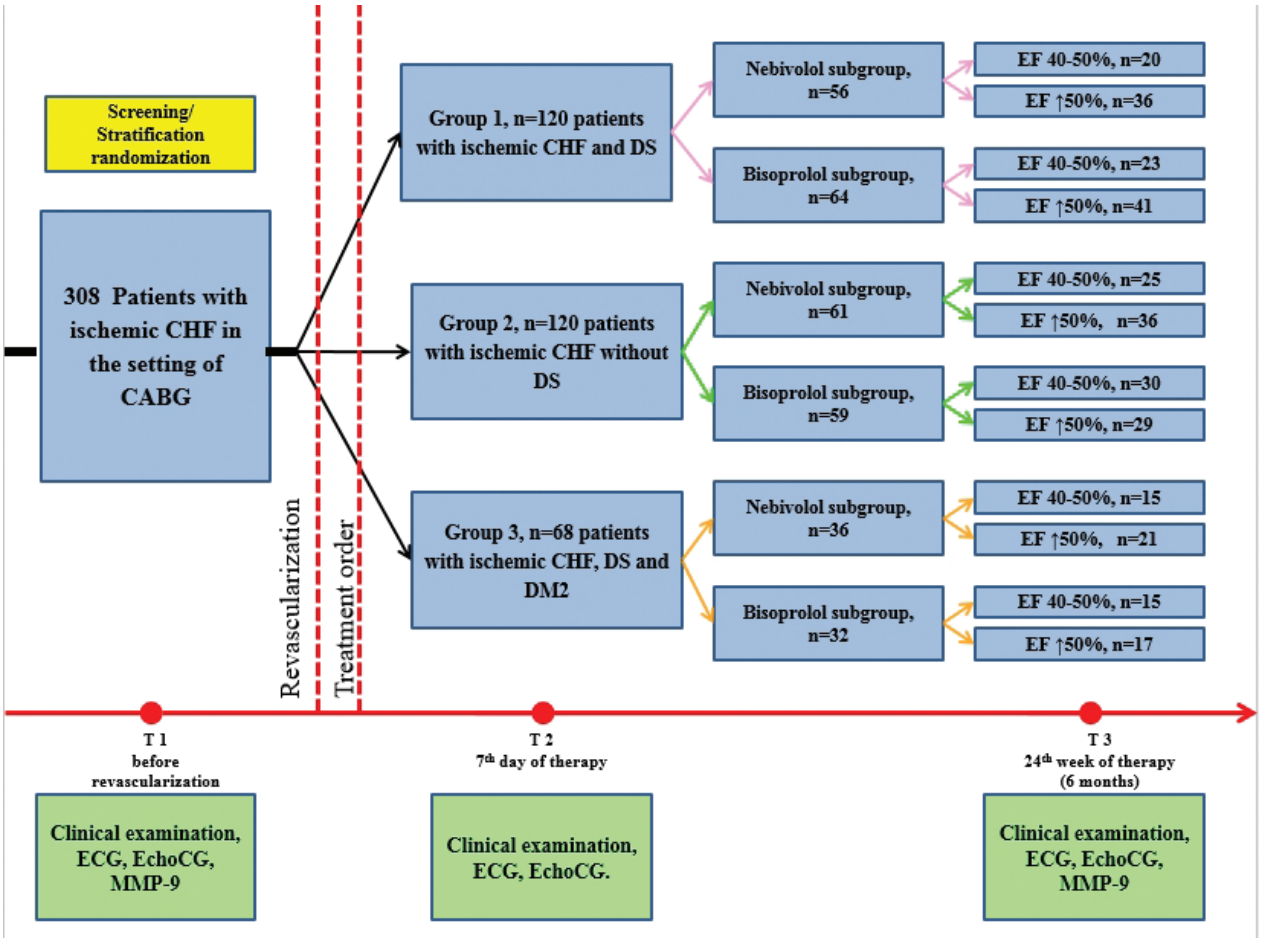

Figure 1. Examination design of patients with ischemic CHF FC I–II with preserved left ventricular ejection fraction after myocardial revascularization by CABG. *Note*: CABG – coronary artery bypass grafting, CHF – chronic heart failure, FC – functional class, DS – dyssynchrony, EF – ejection fraction, ECG – electrocardiography, EchoCG – echocardiography, MMP-9 – metalloproteinase 9

Table 2. Clinical characteristics of the examined groups of patients

Clinical data	Group 1 With mechanical dyssynchrony	Group 2 Without mechanical dyssynchrony	Group 3 With T2DM and mechanical dyssynchrony
Total number of the examined patients, n (%)	120 (100 %)	120 (100 %)	68 (100%)
Men, n (%)	92 (78.9 %)	110 (91.6 %)	36 (52.2 %)
Women, n (%)	28 (23 %)	10 (8.3 %)	32 (47.8 %)
Mean age, years	62 ± 6.6	59 ± 5.1	63 ± 5.2
NYHA CHF FC I, n (%)	47 (37.5 %)	82 (65.8 %)	26 (38.8 %)
NYHA CHF FC II, n (%)	75 (62.5 %)	40 (33.3 %)	42 (61.2 %)
LVEF 40–49 %, n (%)	70 (58 %)	15 (12.5 %)	22 (32.4 %)
LVEF > 50 %, n (%)	50 (41.6 %)	105 (87.5 %)	46 (67.6 %)
QRS msec >120 msec, n (%)	31 (25.5 %)	10 (6.66 %)	15 (22.3 %)
Previous myocardial infarction, n (%)	102 (84 %)	95 (79 %)	59 (86.4 %)
Heart rhythm disorder, n (%)	28 (23.7 %)	32 (26.6 %)	15 (22.8 %)
Ischemic mitral insufficiency up to degree 2, n (%)	59 (49 %)	22 (18.3 %)	27 (40.3 %)

Note: LVEF – left ventricular ejection fraction, NYHA – New York Heart Association, CHF – chronic heart failure, FC – functional class

sonalized approach to the β-blockers therapy in the subgroups of patients formed depending on the LVEF level: subgroups with midrange ejection fraction (40–50%) and with preserved ejection fraction (>50%).

Beta-blockers were prescribed on the 2nd day after CABG. The initial dose of nebivolol (Nebilet, Berlin-Chemie AG, Germany) was 1.25–2.5 mg/day and that of bisoprolol (Concor, Merck KGaA, Germany) – 1.25–2.5 mg/day. The dose titration is presented in Table 3.

In the group of patients with ischemic CHF, DS and comorbid T2DM, the average daily dose of nebivolol 6 months later was 5.25±2.37 mg/day; that of bisoprolol – 5.01±2.89 mg/day. For 6 months, the patients received optimal pharmacotherapy, including calcium antago-

Table 3. The average daily doses of β-blockers (Nebivolol, Bisoprolol) during titration for 6 months in patients with dyssynchrony

Drug	Initial dose	7th day of the therapy	30th day of the therapy	3 months of the therapy	6 months of the therapy
	examination	examination	interview	physician visit, examination	physician visit, examination
Nebivolol, mg/day (n=56)	2.4±0.81	3.91±1.23	4.52±0.98	5.23±1.03	5.11±2.56
Bisoprolol, mg/day (n=64)	2.17±1.03	3.43±1.31	4.56±1.23	5.31±1.65	4.92±2.41

nists from the dihydropyridine group, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB), statins, and antiplatelets. The patients were examined at three stages. The first examination was performed before CABG, the second one – on the 10th day and the third one – 6 months into the course of pharmacotherapy. Physical examination of the patient, ECG, EchoCG, blood sampling, detection of the MMP-9 level in blood plasma were carried out at the first stage (without β-blocker administration) and 6 months into the course of pharmacotherapy. The MMP-9 plasma level was measured at the Test Laboratory Center of the Federal State-Funded Healthcare Institution "Hygienic and Epidemiological Center in Belgorod region", using enzyme immunoassay kit for measuring human MMP-9 (Bender MedSystems GmbH, Austria). The study was performed using an enzyme immunoassay photoelectric analyzer SANRIS, Austria. The quantitative parameters were calculated by constructing a calibration curve using computer software, with the amount expressed in ng/ml.

EchoCG was performed to assess the structures and functions of the heart chambers. Standard pulsed Doppler echocardiography was used to evaluate interventricular mechanical delay (IVMD). The assessment of the intraventricular mechanical dissynchrony was performed by Tissue Doppler Imaging (Tissue Synchronization Imaging, or TSI) using 6 basal and 6 midsegment models (Yu et al. 2005). For each range, the following TSI parameters were calculated: septal lateral delay, septal posterior delay, and basal max delay. The time to peak myocardial systolic velocity in the ejection phase (TS) was measured with reference to the QRS complex. The maximum delay across all 12 segments (TS12) and TS standard deviation (TS-SD) of all 12 LV segments were calculated (Cazeau et al. 2003, Yu et al. 2003).

Statistical data processing was performed using Statistica for Windows.The data are presented as median (Me) and interquartile ranges (25th and 75th percentile ranges). A normality of data distribution was assessed using the Kolmogorov-Smirnov test. For the dependent samples (treatment dynamics), there was used the signs test and the Wilcoxon test, with the preliminary Friedman test if the number of observation points in dynamics was more than 2, were used. The Mann-Whitney test was used for independent samples (distribution into subgroups by feature). Spearman's rank correlation coefficient was used to study the relationship between the variants. Differences were considered significant when $p<0.05$.

Results and discussion

It was found that in patients with DS (in comparison with patients without DS) LV diastolic dimension (LVDD) increased by 9% ($p<0.05$), indexed left ventricular end systolic volume (ESVI) – by 8% ($p<0.05$), left atrium cavity – by 6.5% ($p<0.01$), pulmonary artery systolic pressure (PASP) – by 25% ($p<0.01$). LVEF decreased by 16% ($p<0.001$). Severe diastolic dysfunction of LV, which showed in an increase in E/E' by 21% ($p<0.05$), DT – by 17.6% ($p<0.05$), isovolumetric relaxation time (IVRT) by 13% ($p<0.05$) and a decrease in E/A by 16% ($p<0.01$) and in E' – by 19% ($p<0.01$), was determined (Table 4).

After revascularization, there was an improvement in myocardial dysynchrony indices. It was proved that in the early postoperative period after CABG in the DS group there was an improvement in myocardial synchronicity. Thus, TS12 decreased by 30% ($p<0.01$), TS-SD – by 28% ($p<0.001$), septal lateral delay – by 39% ($p<0.001$), septal posterior delay – by 31% ($p<0.01$), basal max delay – by 36% ($p<0.001$), and IVMD – by 15% ($p<0.05$).

Synchronicity was restored, accompanied by an improvement in LV myocardial contractility by 8% ($p<0.05$) and LV lusitropy (an increase in E/A by 27% ($p<0.01$), a decrease in DT by 14% ($p<0.01$) and in E/E' – by 15% ($p<0.05$)).

The study found that long-term administration of nebivolol in patients with DS decreased EDVI by 8% $p<0.05$), ESVI – by 13% ($p<0.05$), left ventricular mass index (LVMI) – by 12% ($p<0.001$), PASP – by 8% ($p<0.01$), increased LVEF by 10% ($p<0.01$) and E/A – by 19% ($p<0.05$) and decreased DT by 12% ($p <0.05$), improved myocardial synchronicity by reducing IVMD by 15% ($p<0.05$), TS12 – by 28% ($p<0.001$), TS-SD – by 31% ($p <0.01$), septal lateral delay – by 41% ($p<0.001$), septal posterior delay – by 39% ($p<0.01$), basal max delay – by 40% ($p<0.01$) (Table 5).

Long-term administration of bisoprolol showed a decrease in EDVI – by 12% ($p<0.05$), ESVI – by 17% ($p<0.001$), LVMI – by 14% ($p<0.001$), PASP – by 9% ($p<0.01$). LVEF increased by 8% ($p<0.01$), LV lusitropy improved by increasing E/A by 21% ($p<0.01$) and decreasing DT by 7% ($p<0.05$). There was also a decrease in TS12 by 22% ($p<0.05$), in TS-SD by 21% ($p<0.05$) and in basal max delay by 30% ($p<0.05$). It was found that in patients with DS, both nebivolol and bisoprolol had a positive effect on the structural and functional parameters and LV diastolic function. At the same time, there was

Table 4. structural and functional parameters in patients with ischemic chf depending on the presence of myocardial dyssynchrony me (Q_1–Q_3)

Parameters, units of measurement	Point of examination	LV Dyssynchrony n = 120	Without LV dyssynchrony n = 120	p
LV EDVI, ml/m^2	Before CABG	58.99 (51.48–66.48)	60.55 (54.41–68.75)	>0.05
	7th day of the therapy	57.99 (45.29–64.48)	57.79 (47.20–63.75)	>0.05
	p	>0.05	>0.05	>0.05
LV ESVI, ml/m^2	Before CABG	28.04 (20.87–36.35)	25.77 (19.67–32.73)	<0.05
	7th day of the therapy	25.31 (19.76–28.43)	24.39 (18.72–31.23)	>0.05
	p	<0.05	>0.05	<0.05
LVEF,%	Before CABG	48.50 (45.00–54.00)	59.00 (54.50–60.00)	<0.001
	7th day of the therapy	53.50 (48.00–55.00)	57.50 (55.00–60.00)	<0.001
	p	<0.05	>0.05	<0.05
E', msec	Before CABG	0.05 (0.04–0.06)	0.06 (0.06–0.07)	<0.01
	7th day of the therapy	0.06 (0.05–0.07)	0.06 (0.06–0.07)	>0.05
	p	>0.05	>0.05	>0.05
E/A	Before CABG	0.76 (0.64–0.83)	0.82 (0.66–0.96)	<0.01
	7th day of the therapy	0.94 (0.77–1.33)	0.96 (0.94–1.44)	<0.05
	p	<0.01	>0.05	<0.05
E/E'	Before CABG	10.50 (7.44–16.10)	9.20 (7.15–10.42)	<0.05
	7th day of the therapy	10.00 (6.77–13.40)	8.20 (7.52–10.65)	<0.05
	p	<0.05	>0.05	>0.05
DT, msec	Before CABG	224.00 (198.0–275.0)	97.00 (89.00–110.50)	<0.05
	7th day of the therapy	207.00 (184.00–231.00)	202.50 (181.50–211.50)	>0.05
	p	<0.01	>0.05	<0.05

Note: LV – left ventricle, EDVI – indexed left ventricular end diastolic volume, ESVI – indexed left ventricular end systolic volume, LVEF – left ventricular ejection fraction, E – early diastolic tissue velocity, E' – peak early diastolic mitral annular velocity, DT – deceleration time, A – Peak late diastolic velocities

Table 5. the comparative analysis of the effect of the 6-month course of Nebivolol (5.1±2.6 mg/day) and Bisoprolol (4.9±2.4 mg/day) on the structural and functional parameters and dyssynchrony in patients with ischemic chf in the group with myocardial dyssynchrony. Me (Q_1–Q_3)

Parameters, units of measurement	Nebivolol, n=56		Bisoprolol, n=64		p
	Before CABG	6 months of the therapy	Before CABG	After 6 months of the therapy	
	1	2	3	4	1–2/3–4
LV EDVI, ml/m^2	61.00 (51.0–78.0-)	59.41* (50.40–67.00)	55.11 (47.00–69.00)	57.40* (45.92–61.53)	>0.05
LV ESVI ml/m^2	30.00 (22.82–39.21)	26.91* (22.40–32.72)	26.93 (19.83–34.22)	23.50** (16.40–30.71)	>0.05
LVEF, %	48.00 (45.00–57.00)	53.00** (51.00–62.00)	49.00 (46.00–55.00)	54.05** (50.00–60.00)	>0.05
LVMI, g/m	132.11 (112.00–157.20)	117.1*** (102.05–125.34)	123.13 (118.00–141.21)	106.00** (96.00–119.31)	>0.05
PASP, mm Hg	40.00 (38.00–45.00)	36.0** (32.00–40.00)	38.0 (35.00–45.00)	34.0** (31.00–40.00)	>0.05
E/A	0.8 (0.62–1.1)	0.96* 0.96(0.72–1.2)	0.76 (0.64–0.83)	0.83** (0.74–0.98)	>0.05
DT, msec	222.00 (197.0–275.0)	204.00* (132.00–271.00)	234.00 (195.00–272.00)	233.00* (181.00–246.00)	>0.05
TS12, msec	155.00 (124.00–177.00)	108.00*** (89.00–140.00)	146.00 (119.00–183.00)	115.00* (100.00–160.00)	>0.05
TS-SD	50.00 (41.00–65.00)	35.0 ** (28.00–51.00)	45.00 (40.00–65.00)	38.00 (31.00–62.00)	<0.05
Septal lateral delay, msec	91.00 (77.00–120.00)	48.0 *** (20.00–78.00)	92.00 (28.00–129.00)	64.00 (38.00–101.00)	<0.05
Septal posterior delay, msec	78.00 (48.00–119.00)	37.00** (21.00–58.00)	56.00 (48.00–96.00)	41.00 (21.00–79.00)	<0.05
Basal max delay, msec	126.00 (101.00–154.00)	73.00** (47.00–125.00)	126.00 (106.00–135.00)	77.00* (56.00–117.00)	>0.05
IVMD	19.00 (14.0–026.00)	16.00* (10.00–22.00)	18.00 (12.00–22.00)	16.00 (15.00–22.00)	>0.05

Note: *p<0.05, ** p<0.01, *** p<0.001 in comparison with values before CABG, LV – left ventricle, EDVI – indexed left ventricular end diastolic volume, ESVI – indexed left ventricular end systolic volume, LVEF – left ventricular ejection fraction, E – early diastolic tissue velocity, E' – peak early diastolic mitral annular velocity, DT – deceleration time, A – Peak late diastolic velocities, PASP – pulmonary artery systolic pressure, TS12 – all segments max delay, TS-SD – all segments standard deviation, IVMD – inter-ventricular mechanical delay

no significant difference in the effect of these drugs. A comparative analysis of the effect of long-term therapy with nebivolol and bisoprolol on DS revealed statistically significant differences in favor of nebivolol (Table 6). In patients with HFmrEF and DS, there was an increase in LVEF both in case of administering nebivolol (by 18%, p<0.01) and bisoprolol (by 10%, p<0.05). Improvement of LV diastolic function was noted in patients with HFmrEF taking nebivolol (an increase in E/A by 25%, p<0.05, and in DT by 22%, p<0.05). In patients taking bisoprolol with HFmrEF and HFpEF, LV diastolic dysfunction improved in the same way (an increase in the E/A ratio was 21% (p<0.05) and DT by 18.7% (p<0.05), respectively). Long-term administration of nebivolol had a positive effect on the DS progression mainly in patients with HFpEF, which was confirmed by a decrease in TS12 by 30% (p<0.001), TS-SD –by 32% (p<0.01), septal lateral delay – by 56% (p<0.001), septal posterior delay –by 54% (p<0.01), basal max delay – by 51% (p<0.01) and was not determined in patients taking bisoprolol (Table 7).

It was found that in patients without DS after the 6-month pharmacotherapy, the effect of nebivolol showed in a decrease in LVDD by 19% (p <0.01), EDVI – by 17% (p<0.05), PASP – by 9% (p<0.05) and an increase in LVEF by 9% (p <0.05). The positive effect of nebivolol on LV diastolic function was proved, which was showed in an increase in E/A by 19% (p<0.01), E` – by 16% (p<0.05), a decrease in E/E' by 9.8% (p<0.05) and DT – by 12% (p<0.05), and which indicates an improvement in LV lusitropy and LV filling pressure (Table 8).

The administration of bisoprolol (6 months) showed an effect on the reduction of EDVI by 18% (p<0.05), ESVI – by 25% (p<0.01), PASP – by 9% (p<0.01) and an increase in LVEF by 7% (p<0.05), while the effect on the LV diastolic function was not determined.

In patients with HFmrEF without DS taking nebivolol, increased LV lusitropy was more marked compared with patients with HFpEF, (increase in E/A by 24% (p<0.05), decrease in E/E' by 6% (p<0.05) and DT – by 11% (p<0.05). The dynamics of LV diastolic function in patients with HFmrEF and HFpEF taking bisoprolol was the same and had no statistical significance. A significant increase in LVEF in patients with HFmrEF without myocardial dyssynchrony was revealed both when administering nebivolol (10%, p<0.05) and bisoprolol (17%, p<0.05), whereas patients with HFpEF had no significant increase in the LV contractility.

It was found that T2DM was accompanied by an increase in E/A by 11.8% (p<0.05), E/E' – by 16% (p <0.05), DT – by 13.2% (p>0.05), and IVRT – by 8.6% (p>0.05). The indicators of intra-LV dyssynchrony were extended – TS12 by 9.7% (p<0.05), TS-SD by 13,8% (p<0.05), septal lateral delay by 21% (p<0.05), basal maximum delay by 10% (p<0.05); IVMD increased by 21% (p<0.05) (Table 9).

It was determined that the administration of nebivolol (6 months) reduced ESVI by 15% (p<0.05), PASP – by 15% (p<0.01) and LVMI – by 12% (p<0.01), whereas increased LVEF by 10% (p<0.05). There was no significant effect on LV diastolic function. At the same time, the influence on the DS was determined. For example, TS12 decreased by 37% (p<0.01), TS-SD – by 29% (p<0.05), and septal lateral delay –by 53% (p<0.01) (Table 10).

When taking bisoprolol (6 months), there was a decrease in EDVI by 18% (p<0.05), ESVI – by 20% (p<0.01), LVMI – by 11% (p <0.05); LVEF grew by 11% (p<0.01). After 6 months of bisoprolol therapy, the dynamics of diastolic function and DS was not statistically significant. Long-term administration of both nebivolol and bisoprolol in patients with HFmrEF and HFpEF with comorbid T2DM was not found to improve LV diastolic function, which is probably due to the pronounced processes of fibrous degeneration and progressive subclinical LV diastolic dysfunction in this category of patients.

It was proved that in patients with HFpEF with comorbid T2DM nebivolol reduced TS12 by 37% (p<0.01), TS-SD – by 29% (p<0.05), and septal lateral delay – by 53% (p<0.01) (Table 11). In patients with HFpEF and HFmrEF with comorbid T2DM taking bisoprolol, no decrease in dyssynchrony parameters was revealed.

In the study of the fibrosis marker, the MMP-9 level in the blood plasma of patients with ischemic CHF of the general group was found to be 4.7 times higher than that in the control group (p<0.001) (Fig. 2). The concentration of MMP-9 in the group of patients with DS was significantly higher – by 14% (p<0.05) than in patients without DS (Fig. 3). Comorbid T2DM significantly increased MMP-9 level – by 12% (p<0.01) (Fig. 4).

In patients with ischemic CHF before treatment, the correlation between MMP-9 level in blood plasma and the severity of CHF FC (p<0.05) was determined. Correlation between MMP-9 level and EDVI (r=0.27, p<0.01), ESVI (r=0.43, p<0,01), LVMI (r=0.60, p<0.001), LVEF (r=-0.60, p<0.001), parameters of the LV diastolic function: E`1 (r=-0.58, p<0.001), E/A (r=-0.49, p<0.001), DT (r=0.43, p<0.001), IVRT (r=0.50, p<0.0001)), as well as indicators of intra-LV dyssynchrony: TS12 (r=0.54, p<0.001), TS-SD (r=0.49,

Table 6. The Comparative analysis of the effect of long-term therapy (6 months) with Nebivolol and Bisoprolol on myocardial dyssynchrony in patients with ischemic chf in the setting of revascularization. Me (Q_1–Q_3)

Parameters, units of measurement	Nebivolol, %	Bisoprolol, %	Dynamics, %	p
	1	2	1–2	1–2
TS12, msec	28.29	20.51	7.78	>0.05
TS-SD	31.11	18.31	12.8	<0.05
Septal lateral delay, msec	41.02	25.97	15.5	<0.05
Septal posterior delay, msec	39.84	30.19	9.65	<0.05
Basal max delay, msec	42.35	34.28	8.93	>0.05
APEI, msec	-7.14	-8.25	-1.11	>0.05
IVMD	-6.66	2.01	4.65	>0.05

Note: TS12 – all segments max delay, TS-SD – all segments standard deviation, IVMD – inter-ventricular mechanical delay, APEI – Aortic Pre-Ejection Period.

Table 7. The Effect of 6-months therapy with Nebivolol (5.1±2.6 mg/day) on myocardial dyssynchrony in patients with ischemic chf depending on lvef. Me (Q_1–Q_3)

Parameters, units of measuremen	HFmrEF n=20		HFpEF, n=36		p		
	Before CABG	After 6 months of therapy	Before CABG	After 6 months of therapy			
	1	2	3	4	1–2	3–4	1–2/3–4
TS12, msec	155.00 (125.00–190.0)	139.00 (91.00–147.00)	160.00 (123.00–176.0)	98.50 (84.50–117.50)	<0.05	<0.05	>0.05
TS-SD	50.00 (44.00–69.00)	36.00 (29.00–55.00)	52.00 (39.00–64.00)	32.47 (12.63–49.77)	<0.05	<0.01	>0.05
Septal lateral delay, msec	91.00 (77.00–143.00)	48.00 (19.00–79.00)	91.00 (71.00–113.00)	40.00 (24.00–76.00)	>0.05	<0.05	<0.05
Septal posterior delay, msec	96.00 (48.00–126.00)	56.00 (21.00–64.00)	72.00 (48.00–111.00)	36.00 (20.00–43.00)	>0.05	<0.05	<0.05

Note: TS12 – all segments max delay, TS-SD – all segments standard deviation, HFmrEF – chronic heart failure with midrange ejection fraction, HFpEF – chronic heart failure with preserved ejection fraction.

Table 8. The comparative analysis of the effect of long-term therapy with Nebivolol (5.4±1.7 mg/day) and Bisoprolol (4.5±1.6 mg/day) in patients with ischemic chf in the setting of revascularization in the group without myocardial dyssynchrony. Me (Q_1–Q_3)

Parameters, units of measurement	Nebivolol, n=61		Bisoprolol, n=59		p
	Before CABG	After 6 months of the therapy	Before CABG	After 6 months of the therapy	
	1	2	3	4	1–2/3–4
EDVI, ml/m^2	55.96 (50.50–66.21)	51.66* (42.05–61.72)	61.15 (56.00–67.00)	49.42* (41.91–58.55)	>0.05
ESVI, ml/m^2	22.7 (18.21–28.63)	17.2 (14.45–28.33)	25.9 (22.81–29.24)	16.5** (13.44–23.72)	>0.05
LVEF, %	58.00 (55.00–60.00)	61.00* 61.00(57.00–64.0)	58.0 (50.00–60.00)	60.0* 60.00(55.00–54.00)	>0.05
PASP, mm Hg	34.0 (30.0–35.0)	30.0* 30.0(28.0–34.0)	32.0 (30.0–36.0)	28.0** 28.0(27.0–32.0)	>0.05
E/A	0.8 (0.62–0.90)	1.2** (0.91–1.00)	0.8 (0.65–0.91)	0.9 (0.65–1.23)	<0.05
E/E’	9.22 (7.10–10.40)	8.30* 8.3(7.10–9.40)	9.42 (8.48–12.30)	9.35 (6.41–12.00)	>0.05

Note: * p<0.05, ** p<0.01, *** p<0.001 in comparison with values before CABG, EDVI – indexed left ventricular end diastolic volume, ESVI – indexed left ventricular end systolic volume, LVEF – left ventricular ejection fraction, PASP – pulmonary artery systolic pressure, A – Peak late diastolic velocities, E – early diastolic tissue velocity, E’ – peak early diastolic mitral annular velocity

Table 9. Structural and functional parameters in patients with ischemic CHF with comorbid T2DM and myocardial dyssynchrony before revascularization. Me (Q_1–Q_3)

Parameters	CHF with DS and DM2, n=68	CHF with DS and without DM2, n=120
E/A	0.67 (0.62–0.79) *	0.76 (0.64–0.83)
E/E’	12.50 (9.84–19.8) *	10.50 (7.44–16.10)
DT, msec	228.00(197.00–286.00)	220.00(196.00–246.00)
IVRT, msec	115.00(98.00–126.00)	104.00(90.00–116.00)
IVMD	19.00(14.00–23.00)*	15.00(12.00–22.00)
TS12, msec	175.00 (139.00–198.00)*	158.00 (129.00–187.00)
TS-SD	58.00 (38.00–78.00)*	52.00 (36.00–68.00)
Septal lateral delay, msec	115.00 (49.00–142.00)**	91.50 (53.50–114.00)
Septal posterior delay, msec	48.53(26.00–72.00)	68.5 (40.00–115.00)
Basal max delay, msec	138.00 (98.00–174.00) *	124.00 (103.00–144.00)

Note: * p<0.05, ** p<0.01 in comparison with patients without T2DM, E – early diastolic tissue velocity, E’ – peak early diastolic mitral annular velocity, DT – deceleration time, A – Peak late diastolic velocities, TS12 – all segments max delay, TS-SD – all segments standard deviation, IVRT – isovolumetric relaxation time, IVMD – inter-ventricular mechanical delay.

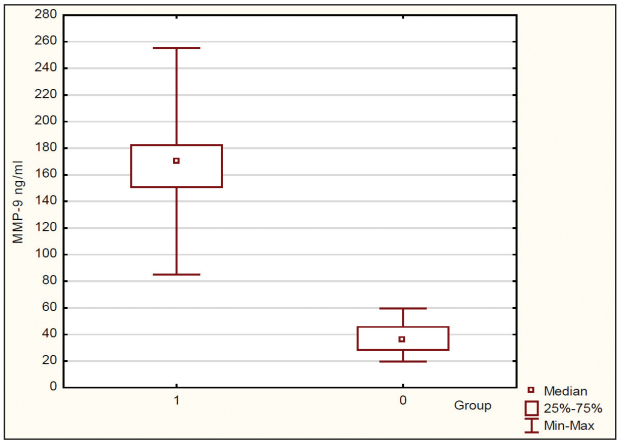

Figure 2. MMP-9 levels in the blood plasma of the general group of patients before revascularization (p<0.001); 0 – reference range, 1– patients with ischemic CHF (n=188). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure

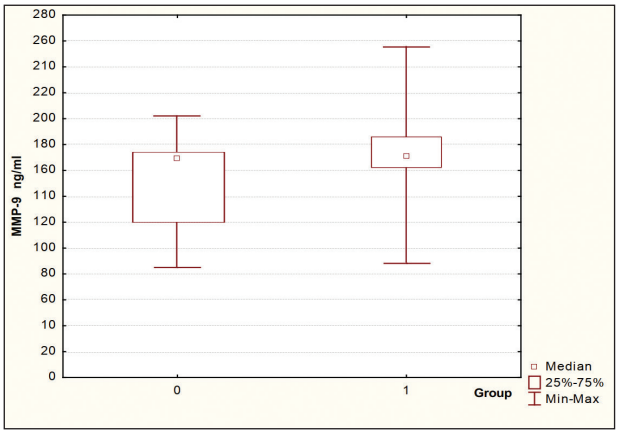

Figure 3. Distribution of MMP-9 levels in the blood plasma of patients with ischemic CHF (p<0.05); 0 – the group without DS (n=58), 1– the group with DS (n=62). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure.

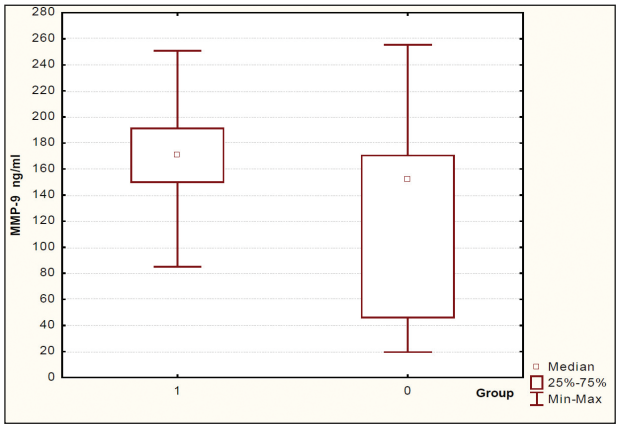

Figure 4. Distribution of MMP-9 levels in the blood plasma of patients with CHF, DS and T2DM and patients with CHF, DS without T2DM (p<0.01); 0 – the group without T2DM (n=62), 1– the group with T2DM (n=68). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure, DS – dyssynchrony, T2DM – type 2 diabetes mellitus.

Table 10. The comparative analysis of the effect of Nebivolol (5.3±2.4 mg/day) and Bisoprolol (5.0±2.9 mg/day) on Structural and Functional parameters and myocardial dyssynchrony in patients with ischemic CHF and comorbid T2DM. Me (Q_1–Q_3)

Parameters, units of measurement	Nebivolol, n=36		Bisoprolol, n=32		p
	Before CABG	After 6 months of the therapy	Before CABG	After 6 months of the therapy	
	1	2	3	4	1–2/3–4
LV EDVI, ml/m²	62.20 (59.40–77.21)	55.51 (55.3–64.4)	58.9 (46.7–76.1)	48.32 41.11–63.92)*	>0.05
LV ESVI, ml/m²	26.10 (23.8–38.9)	22.72 (20.0–28.3)*	25.0 0 (19.4–31.1)	20.00 (16.1–23.9)**	>0.05
LVEF, %	56.00 45.00–59.00)	62.00* (52.00–64.00)	55.00 (46.00–60.00)	57.00* (55.0–65.00)	>0.05
LVMI, g/m²	112.89 (103.18–141.33)	101.16** (91.34–121.20)	124.13 (114.00–141.20)	106.57** (105.00–128.32)	>0.05
PASP, mm Hg	40.00 (37.00–45.00)	34.00** (30.00–40.00)	37.00 (34.00–45.00)	34.00 (32.00–40.00)	<0.05
E/E'	7.40 (6.04–15.90)	9.25 (8.51–15.74)	10.51 (10.20–13.10)	14.40 (10.40–16.60)	>0.05
E/A	0.86 (0.62–1.15)	0.97 (0.71–1.21)	0.78 (0.63–0.81)	0.84 (0.81–0.86)	>0.05
TS12, msec	174.00 (109.00–182.00)	98.50** (63.00–135.00)	136.00 (107.00–176.00)	115.0 (51.00–170.00)	>0.05
TS-SD	55.00 (32.00–63.00)	32.50 * (17.50–47.00)	44.00 (36.00–64.00)	38.00 (19.00–63.00)	<0.001
Septal lateral delay, msec	91.00 (77.00–120.00)	48.00** (20.00–78.00)	92.00 (19.00–128.00)	64.0 (42.00–106.00)	<0.001
Basal max delay, msec	92.00 (43.00–126.00)	82.00 (38.00–125.00)	110.00 (104.00–147.00)	78.00 (58.00–119.00)	>0.05

Note: * p <0.05, ** p <0.01, *** p <0.001 in comparison with values before CABG, E – early diastolic tissue velocity, E' – peak early diastolic mitral annular velocity, DT – deceleration time, A – Peak late diastolic velocities, TS12 – all segments max delay, TS-SD – all segments standard deviation, LV – left ventricle, EDVI – indexed left ventricular end diastolic volume ESVI – indexed left ventricular end systolic volume, LVEF – left ventricular ejection fraction, PASP – pulmonary artery systolic pressure

p<0,001), septal lateral delay (r=0.44, p<0.001), and septal posterior delay (r=0.37, p<0.001) and IVMD (r=0.32, p<0.001) was observed. In patients with comorbid T2DM before treatment, MMP-9 level in the blood plasma correlated with LVEF (r=-0.43, p<0.05), LVMI (r=0.28, p<0.05) and LV volumes (EDVI (r=0.65, p<0.01), ESVI (r=0.57, p<0.01), E` (r=-0.64, p<0.01), E/A (r=-0.59, p<0.01), TS-SD (r=0.69, p<0,05), septal lateral delay (r=0.56, p<0.01)).

As a result of pharmacotherapy with nebivolol (6 months) in patients with ischemic CHF of the general group in the setting of revascularization, there was a significant decrease in the MMP-9 level in blood plasma – by 11% (p<0.01) (Fig. 5), while in the patients of the bisoprolol group, there was an increase in the MMP-9 level in blood plasma by 6.5% (p>0.05) (Fig. 6).

At the same time, the dynamics of lowering of the MMP-9 level in blood plasma in patients treated with nebivolol is significantly higher than in patients treated with bisoprolol (p<0.01) (Table 12). Neither was a dose-dependent effect on reducing the MMP-9 level observed in nebivolol.

After 6 months of nebivolol therapy, a decrease in the MMP-9 level by 7% in the group of patients with DS (p<0.05) and by 3% (p>0.05) in the group of patients without DS was observed (Table 13). There was also a statistically significant, though low, positive correlation between the MMP-9 level and a parameter of intra-LV dyssynchrony – TS12 (r=0.23, p<0.05).

As a result of pharmacotherapy with nebivolol (6 months of administration) in patients with ischemic CHF, T2DM and DS, a significant 13% (p<0.05) de-

Table 11. The effect of 6 months taking Nebivolol (5.3±2.4 mg/day) on LV diastolic function and myocardial dyssynchrony in patients with ischemic CHF and comorbid T2DM depending on the LV ejection fraction. Me (Q_1–Q_3)

Parameters, units of measurement	HFmrEF, n=15		HFpEF, n=21		p
	Before CAB	After 6 months of therapy	Before CABG	After 6 months of therapy	
	1	2	3	4	1–2/3–4
E/A	0.81 (0.54–0.98)	0.83 (0.65–1.04)	0.81 (0.62–1.02)	0.76 (0.67–1.21)	>0.05
E/E’	15.70 (6.4–16.10)	16.0 (15.3–18.6)	7.4 (5.8–14.30)	8.8 (8.3–9.3)	>0.05
TS12, msec	173.00 (140.00–255.0)	166.00 (130.00–170.00)	175.00 (89.00–177.0)	79.00** (52.00–107.00)	<0.05
TS-SD	50.00 (46.00–62.00)	60.00 (36.00–64.00)	60.00 (24.00–65.00)	28.00 ** (17.00–42.00)	<0.05
Septal lateral delay, msec	77.00 (67.00–103.00)	20.00* (12.00–116.00)	84.00 (31.00–107.00)	20.00* (10.00–32.00)	>0.05

Note: * p<0.05, ** p<0.01, in comparison with values before CABG, E – early diastolic tissue velocity, E’ – peak early diastolic mitral annular velocity, DT – deceleration time, A – Peak late diastolic velocities, TS12 – all segments max delay, TS-SD – all segments standard deviation

Table 12. The effect of long-term therapy with Nebivolol (5.46±2.1 mg/day) and Bbisoprolol (5.1±1.9 mg/day) on the dynamics of MMP-9 level in patients with ischemic CHF in the setting of CABG. Me (Q_1–Q_3)

Parameters, units of measurement	Nebivolol (n=96)		Bisoprolol (n=92)		p
	Before CABG	After 6 months of the therapy	Before CABG	After 6 months of the therapy	
	1	2	3	4	1–2/3–4
MMP-9 ng/ml	171.1 (150.2–190.5)	149.8 (142.1–163.1)**	165.4 (150.2–178.1)	167.7 (155.3–173.3)	<0.01

Note: **p<0.01 – significant differences in the group of nebivolol after 6 months of the therapy, CABG – coronary artery bypass grafting.

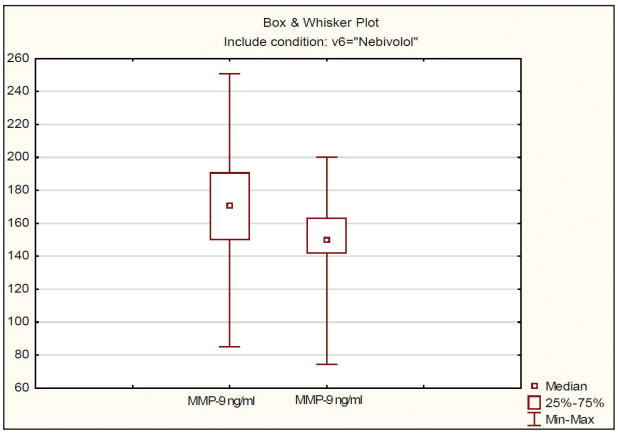

Figure 5. Dynamics of an decrease in MMP-9 level in the blood plasma of patients with ischemic CHF in the setting of revascularization within 6 months of nebivolol therapy (p<0.01) (n=96). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure, DS – dyssynchrony, T2DM – type 2 diabetes mellitus

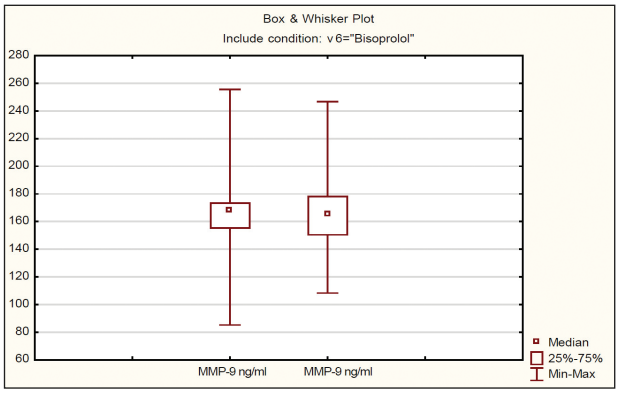

Figure 6. Dynamics of a decrease in MMP-9 level in the blood plasma of patients with ischemic CHF in the setting of revascularization within 6 months of bisoprolol therapy (p>0.05) (n=92). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure, DS – dyssynchrony, T2DM – type 2 diabetes mellitus

Table 13. The Effect of 6-month therapy with Nebivolol on the MMP-9 level in the groups of patients with DS and without DS. Me (Q_1–Q_3)

Parameters, units of measurement		Group DS (n=32)	Group without DS (n=28)	p
		1	2	1–2
MMP-9, ng/ml	Before CABG	171.0 (160.0–185.1)	158.8 (120.0–173.1)	<0.05
	After 6 months of therapy	160.5 (144.7–172.1)	154.7 (138.9–169.7)	>0.05
	p	<0.05	>0.05	<0.05

Note: **p<0.01 – significant differences in the group of nebivolol after 6 months of the therapy, CABG – coronary artery bypass grafting, DS – dyssynchrony, MMP-9 – metalloproteinase 9

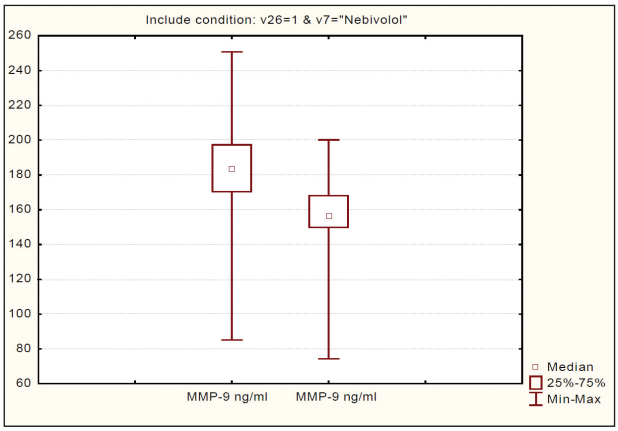

Figure 7. The reduction dynamics of the MMP-9 level during 6-month therapy with nebivolol in patients with ischemic CHF and comorbid T2DM and DS ($p<0.05$) (n=36). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure, DS – dyssynchrony, T2DM – type 2 diabetes mellitus

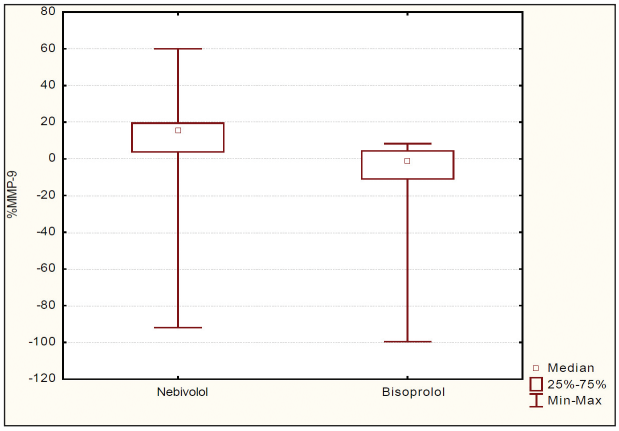

Figure 8. The comparison of reduction dynamics of the MMP-9 level in the nebivolol (n=36) and bisoprolol (n=32) groups in patients with ischemic CHF and comorbid T2DM and DS ($p<0.01$). *Note*: MMP-9 – metalloproteinase 9, CHF – chronic heart failure, DS – dyssynchrony, T2DM – type 2 diabetes mellitus

crease in the MMP-9 level in blood plasma was observed (Fig. 7), which was not observed in patients taking bisoprolol – dynamics decreased by 3% ($p<0.05$). At the same time, the reduction dynamics of the MMP-9 level in blood plasma of patients treated with nebivolol was significantly higher in comparison with that in patients treated with bisoprolol ($p<0.01$) (Fig. 8). Neither was a dose-dependent effect on reducing the MMP-9 level observed in nebivolol.

Thus, our study proved that nebivolol has a pleiotropic effect of inhibiting the MMP-9 level, by influencing the alternative pathway of independent synthesis of angiotensin II by chemases. As a result, nebivolol has an antifibrotic effect.

Resume

As of today, there have not been wnough studies aimed at examining pharmacotherapy for patients with ischemic HFmrEF and HFpEF after CABG, including in combination with type 2 DM. When analyzing medical literature, some sporadic papers were found, which described experimental preclinical studies that proved a positive effect of β-blockers on LV diastolic dysfunction in heart failure by reducing the degree of myocardial fibrosis. X. Zhou et al. (2010) showed that nebivolol had improved diastolic relaxation and slowed LV remodeling by reducing interstitial fibrosis in insulin-resistant rats by activating endothelial NO synthase, reducing free radical concentrations of reactive oxygen species (ROS) and oxidative stress. The study by Y. Fang et al. (2011) demonstrated a more pronounced, when compared to metoprolol, ability of nebivolol to improve LV hemodynamics and LV diastolic function by activating endothelial NO synthase, increasing NO bioavailability and improving coronary vasorelaxation. L. Ma and co-authors in their study (in the transgenic rat model) confirmed the ability of a β-blocker nebivolol to improve diastolic function and to slow down the process of LV remodeling, reducing interstitial fibrosis by reducing myocardial oxidative stress (Ma et al. 2012). However, there have been no studies aimed at investigating either the effect of long-term pharmacotherapy with nebivolol on cardiac dyssynchrony, LV diastolic function, or on the violation of collagen metabolism by suppressing MMP-9 in patients with ischemic HFmrEF and HFpEF in the setting of myocardial revascularization.

The present study for the first time proved the effectacy of long-term administration of β-blocker nebivolol to treat dyssynchrony in patients with ischemic HFpEF in the setting of revascularization. Besides, the study proved a positive impact of nebivolol on LV remodeling and diastolic function predominantly in patients with ischemic HFmrEF in the setting of revascularization without myocardial DS. While conducting the study, the feasibility of a personalized approach to pharmacotherapy in patients with comorbid T2DM was justified, and for the first time it was discovered that a pharmacotherapy with β-blocker nebivolol influenced the course of DS in such patients.

An important finding was a proven effect of long-term administration of nebivolol on the reduction of the MMP-9 level in patients with ischemic CHF in the setting of revascularization, including patients with comorbid type 2 diabetes mellitus. The experimental data obtained during the study allow considering MMP-9 as a biomarker of cardiac remodeling and DS. MMP-9 is also an additional criterion confirming the presence of myocardial fibrosis and can be used as a pharmacological target in the treatment of patients with CHF and CHD, including patients with comorbid type 2 diabetes mellitus in the early and advanced time after myocardial revascularization.

Conclusion

1. In patients with ischemic chronic heart failure, the presence of myocardial dyssynchrony is a predictor of deterioration in the CHF progression and manifests in impaired structural (left ventricular and left atrial enlargement and expansion), hemodynamic (pulmonary hypertension) and functional (decrease in contractility and severe diastolic dysfunction of the left ventricle) heart parameters. The prognostic value of metalloproteinase-9 for cardiac dyssynchrony and the severity of chronic heart failure was proved.
2. The administration of nebivolol for 6 months according to the titrating regimen at the average dose of 5.1±2.6 mg/day results in the restoration of myocardial synchronicity in patients with ischemic chronic heart failure in the setting of revascularization, to a greater extent – in patients with preserved ejection fraction, which is confirmed by decreased intraventricular dyssynchrony: TS-SD dissynchrony index decreased by 32%, TS12 maximum delay – by 30%, septal lateral delay – by 56%, septal posterior delay – by 54% and basal maximum delay – by 51%. After 6 months of therapy, nebivolol reduces the metalloproteinase-9 level in blood plasma by 11% ($p<0.01$) in patients of the general group and by 7% ($p<0.05$) in patients with dyssynchrony, which is not observed in patients taking bisoprolol.
3. Six-month administration of nebivolol according to the titrating regimen at the average dose of 5.4±1.7 mg/day improves the left ventricle diastolic function in patients with ischemic chronic heart failure in the setting of revascularization without myocardial dyssynchrony, to a greater extent – in patients with midrange ejection fraction, which is confirmed by an increase in the E/A ratio by 24% ($p<0.05$), a decrease in E/E' by 6% ($p<0.05$) and DT – by 11% ($p<0.05$), which is not observed in patients taking bisoprolol.
4. Patients with ischemic chronic heart failure and comorbid type 2 diabetes mellitus had severe LV diastolic dysfunction, severe myocardial dyssynchrony and high levels of metalloproteinase-9.
5. Long-term administration (6 months) of nebivolol and bisoprolol has no effect on the course of left ventricular diastolic dysfunction in patients with ischemic chronic heart failure in the setting of myocardial revascularization with comorbid type 2 diabetes mellitus and myocardial dyssynchrony. Administration of nebivolol for 6 months at the average dose of 5.3±2.4 mg/day improves intraventricular synchronicity in patients with chronic heart failure with preserved ejection fraction in the setting of revascularization in combination with type 2 diabetes mellitus, reducing the level of metalloproteinase-9 in blood plasma by 13% ($p<0.05$).

List of abbreviations

A – Peak late diastolic velocities
ACE inhibitors – angiotensin-converting enzyme inhibitors
ARB – Angiotensin II Receptor Blocker
ARB – angiotensin II receptor blockers
CABG – coronary artery bypass grafting
CHD – coronary heart disease
CHF – chronic heart failure
DD – diastolic dysfunction
DS – dyssynchrony
DT – deceleration time
E – early diastolic tissue velocity
E' – peak early diastolic mitral annular velocity
EchoCG – echocardiography
EDVI – indexed left ventricular end diastolic volume
ESVI – indexed left ventricular end systolic volume
FC – functional class
HFmrEF – chronic heart failure with midrange ejection fraction
HFpEF – chronic heart failure with preserved ejection fraction
HFrEF – chronic heart failure with reduced ejection fraction
Intra-LV dyssynchrony – intra-ventricular mechanical dyssynchrony
IVMD – inter-ventricular mechanical delay
IVRT – isovolumetric relaxation time
LAD – left atrial diameter
LV – left ventricle
LVDD – LV diastolic dimension
LVEF – left ventricular ejection fraction
MMP-9 – metalloproteinase 9
PASP – pulmonary artery systolic pressure
T2DM – type 2 diabetes mellitus
TDI – tissue Doppler imaging
TS12 – all segments max delay
TSI – Tissue Synchronization Imaging
TS-SD – all segments standard deviation

Conflict of interests

The authors state no conflict of interest concerning with the present submitted manuscript.

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Author contributions

- **Irina V. Askari,** postgraduate student, Department of Intermediate Level Therapy, e-mail: askari.irina@mail.ru. **ORCID ID** 0000-0002-8307-6101. The author provided the idea of research, analyzed the results and made conclusions.

- **Olga A. Osipova**, Doctor of Medical Sciences, Associate Professor, Department of Hospital Therapy, Belgorod State National Research University, Belgorod, Russia; e-mail osipova@bsu.edu.ru. **ORCID ID** 0000-0002-7321-6529. The author provided the idea of research, analyzed the results and made conclusions.