Treatment of Acute Coronary Syndromes in Patients with Type 2 Diabetes Mellitus with β-Adrenoblockers and Angiotensin-Converting Enzyme Inhibitors: Cardiohemodynamic Effects and Impact for Prognosis

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Long-term oral treatment of patients with acute coronary syndromes and type 2 diabetes mellitus with β-adrenoblockers and angiotensin-converting enzyme inhibitors is associated with positive, though ambiguous changes in the left-ventricular structure and function. These changes should be the reason for choosing optimal therapy ensuring better prognosis in this patient population.

Key Words: *acute coronary syndromes; diabetes mellitus; β-adrenoblockers; angiotensin-converting enzyme inhibitors*

Effective treatment of diabetes mellitus (DM) is a key problem in many branches of medicine because of rapidly growing prevalence of this pathology [7]. Cardiovascular complications (myocardial infarction, brain stroke, lower limb gangrene) are the main causes of death in patients with type 2 DM. The incidence of coronary disease in these patients is 2-4-fold higher than in non-diabetics of the same age. DM twofold increases the risk of coronary death [5,6].

Several causes of deterioration in coronary patients with DM are known. DM is associated with earlier and more extensive atherosclerotic involvement of vessels, including coronary arteries; myocardial infarction is often almost asymptomatic and not diagnosed in time. The systolic and diastolic cardiac functions in diabetics are deteriorated because of impairment of myocardial energy metabolism and more pronounced fibrosis, as well as because of cardiac autonomic neuropathy. This latter condition also contributes to the risk of sudden arrhythmic death because of unstable autonomic regulation. Oxidative stress characteristic of DM leads to endothelial damage, impairs vasodilating capacity, increases functional load to the heart, and promotes left-ventricular (LV) hypertrophy. Decreased fibrinolysis in combination with increased platelet aggregation and blood fibrinogen level augment the risk of clot formation [2].

Modern drug therapy of acute coronary syndromes includes β-adrenoblockers and angiotensin-converting enzyme (ACE) inhibitors; the efficiency of these drugs is considered to be proven [1,8]. On the other hand, cardiohemodynamic effects of these drugs and their impact for the prognosis in diabetics developing acute coronary syndrome remain little studied.

We evaluated the cardiohemodynamic effects of β-adrenoblockers and ACE inhibitors and their impact for the prognosis in patients with myocardial infarction or unstable angina developing against the background of 2 DM.

MATERIALS AND METHODS

The study was carried out in 385 patients (261 men and 124 women) aged 39-74 years (mean age 62.3±4.8 years) hospitalized at Cardiology Department No. 1,

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Krasnodar Municipal Clinical Emergency Hospital. Using clinical, biochemical, and instrumental methods, *Q*-wave myocardial infarction was diagnosed in 140 cases and unstable angina in 245 cases. Patients with contraindications precluding the use of β-adrenoblockers and/or ACE inhibitors, severe visceral diseases with dysfunctions, which could distort the results of the study, permanent atrial fibrillation, and individuals aged over 75 years were not included in the study. In addition to the standard therapy, patients with myocardial infarction were prescribed (at random) bisoprolol in a titered daily dose of 5-10 mg (group 1, n=35), enalapril in a daily dose of up to 10-20 mg (group 2, n=35), or combination of these drugs (group 3, n=35). Patients with unstable angina received, in addition to the standard therapy, CR/XL metoprolol in a daily dose of 100-200 mg (group 4, n=35), bisoprolol in a daily dose of 5-10 mg (group 5, n=35), carvedilol in a daily dose of 25-50 mg (group 6, n=35), captopril in a daily dose of 37.5-75 mg (group 7, n=35), perindopril in a daily dose of 4-8 mg (group 8, n=35), or a combination of bisoprolol and perindopril (group 9, n=35). Patients treated with atenolol (daily dose of 50-100 mg) for myocardial infarction (group 10, n=35) or unstable angina (group 11, n=35) served as controls.

M- and B-mode echocardiography and pulse wave Doppler-echocardiography on a Combison 420 ultrasonic device with a 3.5 MHz pickup (standard method) were carried out in all patients after stabilization of the status during hospital treatment and after 6 months of continuous therapy. The thickness of the ventricular septum and posterior wall and end-diastolic and end-systolic sizes of the LV were measured. The end-diastolic and end-systolic volumes were calculated using Simpson's method and used in the common formula of LV ejection fraction. LV myocardial weight was calculated using Devereux formula. LV diastolic function was evaluated by Doppler transmitral spectrum (maximum bloodflow velocities during early and atrial filling were measured and their ratio was calculated). All patients were ranked by the structure of LV diastolic filling, depending on the severity of condition: first (normal), second (rigid), third (pseudonormal), and fourth (restrictive type of diastolic LV dysfunction). The pseudonormal type was differentiated from the norm using Valsalva's test.

During 6 months of controlled therapy, the following parameters were recorded: cardiovascular mortality, number of repeated infarctions (in patients with myocardial infarction), number of repeated hospitalizations for unstable angina (in patients with unstable angina), and new cases of myocardial infarction.

The significance of differences in the parameters by quantitative signs was evaluated using Student's t test; the differences were considered significant at $p<0.05$.

RESULTS

Randomized groups of patients with myocardial infarction (1, 2, 3, and 10) and unstable angina (4, 5, 6, 7, 8, 9, and 11) were similar by demographic, clinical, and echocardiographic parameters. The groups of patients with myocardial infarction virtually did not differ by the localization of the infarction zone and the number of thrombolytic therapy courses.

Oral treatment with bisoprolol, enalapril, or their combination for 6 months after the development of

TABLE 1. Dynamics of Main Echocardiographic Parameters of LV in Patients with Myocardial Infarction Treated with Bisoprolol, Enalapril, and Their Combination ($M\pm m$)

Treatment protocol, group	EDVI, ml/m²	ESVI, ml/m²	EF, %	MWI, g/m²	DF rank, Units
Group 1					
initially (n=35)	104.8±6.7	53.0±3.5	49.4±2.2	156.1±7.3	3.27±0.16
bisoprolol (n=33)	96.3±5.9	42.3±3.0*	56.1±2.9*	148.7±6.9	3.25±0.15
Group 2					
initially (n=35)	106.3±6.5	54.2±3.4	49.0±1.8	159.1±7.7	3.39±0.18
enalapril (n=33)	92.8±5.3*	43.5±2.7*	53.1±2.4	141.6±6.3*	2.95±0.14*
Group 3					
initially (n=35)	107.5±7.0	52.9±3.6	50.8±2.1	160.2±7.9	3.36±0.15
bisoprolol+enalapril (n=34)	90.3±5.1*	35.9±2.6*	60.2±3.4*	138.9±6.0*	3.04±0.11*
Group 10 (control)					
initially (n=35)	105.4±7.2	53.6±3.2	49.1±2.0	157.9±6.8	3.31±0.12
atenolol (n=32)	106.3±6.8	51.8±3.4	51.3±2.3	159.2±7.0	3.28±0.14

Note. Here and in Table 2: EDVI: end-diastolic volume index; ESVI: end-systolic volume index; EF: ejection fraction; MWI: myocardial weight index; DF: diastolic function; *$p<0.05$ compared to the initial value.

myocardial infarction was associated with a significant increase in the mean values of LV ejection fraction (by 13.5, 8.3, and 18.6%, respectively). In patients treated with atenolol this parameter changed negligibly (4.4%). The mean ranking parameters of the LV diastolic function decreased significantly (improved) after treatment with enalapril alone and in combination with bisoprolol, but not after bisoprolol or atenolol monotherapy (Table 1). For 6 months of controlled therapy 3, 3, 1, and 4 patients, respectively, developed repeated myocardial infarctions; 2, 2, 1, and 3 patients died from cardiovascular causes in groups 1, 2, 3, and 10, respectively.

In patients with a history of unstable angina the LV ejection fraction appreciably increased after 6 months of therapy with CR/XL metoprolol, bisoprolol, carvedilol, captopril, perindopril alone or in combination with bisoprolol (by 12.5, 14.6, 16.3, 9.9, 10.2, and 18.8%, respectively). Atenolol therapy only slightly increased this parameter (3.5%). The mean ranking parameters of LV diastolic function decreased significantly after therapy with carvedilol, captopril, perindopril alone and in combination with bisoprolol, but not CR/XL metoprolol, bisoprolol, and atenolol (Table 2). For 6 months of therapy 9, 9, 8, 11, 8, 6, and 13 patients from groups 4, 5, 6, 7, 8, 9, and 11, respectively, were hospitalized for the coronary syndrome, 4, 4, 4, 5, 3, 2, and 6 patients developed myocardial infarction, and 2, 2, 2, 3, 2, 1, and 4 patients died from cardiovascular events, respectively.

Hence, long therapy with the majority of β-adrenoblockers (except atenolol) and ACE inhibitors leads to an appreciable improvement of the LV systolic function in patients with myocardial infarction or an episode of unstable angina in the presence of type 2 DM. The difference seems to be due to hydrophilic nature of atenolol, which makes this drug inferior to lipophilic β-adrenoblockers as regards the capacity to accumulate in tissues and exert a cardioprotective effect [4]. All ACE inhibitors and adrenoblocker carvedilol improve significantly the LV diastolic function in patients with acute coronary syndromes. Our data on failure of the majority of β-adrenoblockers to improve the LV diastolic function are in line with the data of other scientists [3]. It seems that the cardiodynamic effects of ACE inhibitors should be regarded as a characteristic of this entire class of drugs, but individual effects of β-adrenoblockers in patients with acute coronary syndromes in the presence of type 2 DM should be taken into consideration. Combined therapy with β-adrenoblockers and ACE inhibitors provides a pronounced improvement of the systolic and an appreciable improvement of the diastolic function of LV. The decrease in the diastolic and systolic

TABLE 2. Dynamics of Main Echocardiographic Parameters of LV in Patients with Unstable Angina Treated with β-Adrenoblockers, ACE Inhibitors, and Their Combination (*M±m*)

Treatment protocol, group	EDVI, ml/m²	ESVI, ml/m²	EF, %	MWI, g/m²	DF rank, Units
Group 4					
initially (*n*=35)	98.7±6.5	47.9±2.6	51.5±1.3	150.3±7.1	2.94±0.13
CR/XL metoprolol (*n*=33)	91.3±5.8	38.4±2.2*	57.9±1.6*	142.1±6.5	2.90±0.11
Group 5					
initially (*n*=350)	95.2±6.3	46.6±2.7	51.1±1.4	146.9±6.7	2.89±0.14
bisoprolol (*n*=33)	88.7±5.6	36.7±2.0*	58.6±1.6*	139.5±6.1	2.92±0.13
Group 6					
initially (*n*=35)	100.3±6.7	48.5±2.4	51.6±1.2	154.0±6.8	2.84±0.15
carvedilol (*n*=33)	90.9±5.7	36.4±1.9*	60.0±1.5*	143.2±6.4	2.53±0.12*
Group 7					
initially (*n*=35)	96.7±5.9	47.6±2.0	50.8±1.7	149.6±7.0	2.86±0.10
captopril (*n*=32)	89.3±5.5	39.5±2.3*	55.8±1.6*	141.7±6.2	2.58±0.12*
Group 8					
initially (*n*=35)	99.2±6.0	49.1±2.5	50.5±1.3	153.6±7.2	2.92±0.14
perindopril (*n*=33)	86.7±5.4	38.4±2.2*	55.7±1.4*	144.9±6.0	2.52±0.11*
Group 9					
initially (*n*=35)	97.3±6.6	47.0±2.6	51.7±1.2	150.2±6.9	2.83±0.10
bisoprolol+perindopril (*n*=34)	82.1±5.3*	31.7±1.8*	61.4±1.5*	138.7±5.8	2.40±0.09*
Group 11 (control)					
initially (*n*=35)	95.8±6.4	46.1±2.5	51.9±1.4	148.6±6.6	2.90±0.13
atenolol (*n*=31)	96.3±6.5	44.6±2.4	53.7±2.4	150.7±6.8	2.94±0.12

volumes, LV hypertrophy, recovery of LV systolic and diastolic functions can be important factors improving the prognosis for patients with acute coronary syndromes in the presence of type 2 DM. Little number of final results does not allow us to make final conclusions about the effects of the treatments used, but a trend to a decrease in the number of complications during combined therapy seems to be a regularity.

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