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Changes of ejection fraction and left ventricular function by the carvedilol use in patients with myocardial infarction and comorbid heart failure on the stage of medical rehabilitation after myocardial infarction

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Abstract
In comparison with the right ventricle, the left ventricle is more muscular, so it's walls are roughly thicker that allows it performing its pumping function under higher pressure respectively roughly by 5 times that provides sufficient blood ejection into aorta. The left ventricle (LV) takes on higher functional exercise than other parts of the heart and therefore tends more often to have pathologic changes. Hence it becomes clear that clinical indications and prognostic significance will be more intense dependent on the functional state of the LV.

A cause of impaired myocardial contractile function is its remodeling that in its turn may have different extents. Its manifestation depends on neurohormonal activation that is noticed after an infarction, as well as on stronger stretch of LV; the result is heart muscle increased oxygen demand. Neurohormone activation occurs at first for stabilizing of heart activity and blood pressure, but eventually its nature becomes pathological.

On the basis of our results of 3-months observation of rehabilitating patients after myocardial infarction, collecting patients' complaints, laboratory and instrumental examinations it is possible to make a conclusion about that that there are medications helping to improve myocardium functional state significantly, particularly the left ventricle. One of such medications is carvedilol, which was included in the treatment scheme of patients from the studied group.

Keywords: myocardial infarction, heart failure, carvedilol, ejection fraction, stress echocardiography

Introduction
According to WHO data, Ukraine is a country №1 in Europe and №2 in the world in cardiovascular mortality rate [13]. When European countries already combat this problem actively, then in Ukraine this is a cause of 67% deaths as before [14]. Each second Ukrainian faces cardiovascular diseases. Last year CVD took lifes of 392 thousand Ukrainians [14]. It is known that a half of people with heart failure die within 4 years, and among patients with severe HF, mortality reaaches 50% during next year [Guidelines of Ukrainian Association of Cardiology].

One of main components of patients' well-being after myocardial infarction (MI) and rehabilitation period delay is forming of chronic heart failure (CHF) or intensification of its clinical picture (increasing of HF stage according to N. D. Strazhesko and V. H. Vasilenko), in other words cardiac remodeling. That is after myocardium damage at the start that causes some amount of normally functioning cardiomyocytes loss, CHF severity intensifies due to the remodeling while causing worsened prognosis for the patient [4].

The patients, who received a qualified medical aid, stay alone in the posthospitalization period; continue living, working, making families, bearing children. So beside other tasks it a task of adequate rehabilitation and preserving left ventricular contractile function to provide maximum normal conditions of patient's vital activity after myocardial infarction remains extremely important [2-8-9-10].

Aim of the research
Studying influence of carvedilol on left ventricular ejection fraction in the rehabilitation period in patients with myocardial infarction and heart failure.

Materials and Methods

We examined 40 patients that had STEMI and NSTEMI and developed heart failure of different functional classes because of this. Full clinical examination of 40 patients (25 males and 15 females) was conducted. The diagnosis of heart failure was made by full examination. All patients were randomly divided into two groups 20 people each: control and study one. The patients from the control group received standard treatment of heart failure: diuretics, statins, digoxin, aspirin, anticoagulants, beta-blockers (Except carvedilol), and ACE inhibitors/sartans. All medications were administered in individually adjusted doses. All patients of the study group got carvedilol in individually adjusted doses on the background of basic therapy. At first carvedilol was administered in dose 3.125 mg/day; by titration the dose was made 25-50 mg/day; an average final dose was (27.5 ± 9.4) mg/day. At the request, nitrates were administered to 42.3% patients, and loop diuretics to 1.2% patients (within 2 months of monitoring). Hereafter, there was no need in administering of additional medications. Both groups were comparable in gender and age aspects. The follow-up lasted 3 months. At the moment of patients screening into the study, in 1 and 3 months it was performed clinical examination following general rules, recording of main complaints, echo monitoring following a standard protocol on the ultrasound system «Sunscape S11». Statistical processing of research results was done in the program «Microsoft Excel Access». Average values, their percental portions and Student's test were calculated. Data measurements of patients from the study and control groups were compared, as well as values within each group on different stages of the research. The values were considered statistically valid, when values difference was by $p < 0.05$.

Results of the research and their discussion

The examined patients that were administered additional individually adjusted carvedilol doses presented significantly improved clinics, complaints were reduced and life quality was improved comparing to the control group of patients, who did not take this medication.

At the start of the treatment, the most common complaint from the patients was pain syndrome and dyspnea at rest as well as by physical examinations. At the end of our research, we saw that these complaints decreased only by a half in the control group (Table 1.1), meanwhile in the study group the percent of patients pointing complaints decreased drastically (85% at the start of the study and 15% at the end for chest pain, and 90% and 10% for dyspnea respectively). Similar tendencies were characteristic for such complaints, as irregularities in heart activity, general weakness and fast tiredness.

Table 1.1: Values dynamics in patients with myocardial infarction and heart failure in the process of rehabilitation (M±m)

Value, measurement unit	Before treatment (n=20)	1 month (n=20)	3 months (n=20)
The control group			
Chest pain	85% (17)	75% (15)	40% (8)
Dyspnea	90% (18)	75% (15)	45% (9)
Palpitation	65% (13)	45% (9)	20% (4)
Nausea	45% (9)	30% (6)	30% (6)
Excessive perspiration	80% (16)	65% (13)	40% (8)
The study group			
Chest pain	85% (17)	65% (13)	15% (3)
Dyspnea	90% (18)	55% (11)	10% (2)
Palpitation	65% (13)	40% (8)	10% (2)
Nausea	40% (8)	25% (5)	15% (3)
Excessive perspiration	15% (3)	5% (1)	0

Note: 1. Percent in each patient group specified.
2. In parentheses absolute numbers specified.

The percent of patients of the study group noticing nausea at the start decreased almost by three times. In the study group were no patients complaining on excessive perspiration, meanwhile in the control group there were 40% of such patients in three months of treatment.

Therefore, administration of carvedilol improved significantly clinical course of rehabilitation period of patients with myocardial infarction and heart failure, what was caused by multifaceted influence of this agent on the human body.

Cardiomyocytes inotropic function in the patients of the study group could be improved significantly according to echocardiographic parameters data compared to echocardiographic data before treatment with carvedilol (table 1.2).

Table 1.2: Values dynamics of hemodynamics in patients with myocardial infarction and heart failure in the process of rehabilitation (M±m)

Value, measurement unit	The control group (n=20)		The study group (n=20)	
	Before treatment	1 month	Before treatment	1 month
EDV, ml	190.40±1.20	188.30±1.20	192.75±0.87	186.55±0.82
		$P_1>0.5$		$P_1>0.5$
ESV, ml	155.20±23.10	149.50±22.10	153.64±27.64	127.50±24.87
		P1>0.1		P1>0.5
EDD, cm	6.10±0.13	6.00±0.21	5.80±0.11	6,00±0.13
		$P_1<0.02$		$P_1<0.02$
ESD, cm	4.90±0.25	4.50±0.26	4.80±0.15	4.70±0.16
		P1>0,5		P1>0.5
Left ventricular posterior wall thickness, cm	1.20±0.08	1.20±0.05	1.18±0.06	1.10±0.04
		$P_1>0.2$		$P_1>0.2$

Interventricular septum thickness, cm	1.10±0.04	1.20±0.06	1.09±0.05	1.04±0.04
		P_1>0.5		P_1>0.5
SV, ml	81.34±3.10	83.50±2.60	80.85±4.00	86.65±3.00
		P_1>0.2		P_1>0.2
Left atrial size, cm	4.30±0.40	4.20±0.50	4.10±0.20	4.10±0.20
		P_1>0,5		P_1>0.5
Right ventricular size, cm	3.60±0.09	3.60±0.30	3.30±0.08	3.20±0.100
		P_1>0,5		P_1>0.5
EF, %	24.60±3.40	26.40±2.70	21.70±3.60	30.30±3.70
		P_1<0.02		P_1<0.02

Note: Probability of indices difference comparing to values: p_1 – before treatment, p_2 – in 1 month of treatment.

Myocardial pump function is provided in two steps: in systole and diastole. The mirror image of myocardial functional capability is its contractile capability that provides cardiac output. Amount of blood ejected by the heart in one contraction is called systolic or stroke volume (SV) and is measured from minute blood volume and heart rate. Changes in the end systolic volume (ESV) in the process of treatment with carvedilol mostly catch the eye. When in the beginning of the research it was (153.64±27.64) ml in this category of patients, then after the first and third months of treatment, it became (127.50±24.87) ml (P1<0.05 before the start of treatment) and (120.50±20.10) ml (P2<0.05 before the start of treatment) respectively (table 1.3). As a comparison, ESV in patients of the study group was (155.20±23.10) ml and (149.50±22.10) ml, P1>0.1 after the first month of treatment and (141.30±21.10) ml after the third one. At the end of the study, ESV value in this group changed significantly in relation to data at the start of treatment, but the change was not statistically significant in relation to data after the 1st month of treatment. Similar patterns were characteristic for EDV dynamics.

Stroke volume and ejection fraction values increased significantly in the group of the patients that had taken carvedilol. So, in the beginning of the research they were (80.85±4.00) ml and (21.70±3.60) % respectively, and in three months (92.40±4.00) ml and (36.00±2.80) % respectively. Pointed dynamics was statistically significant, P<0.05. Stroke volume and ejection fraction values underwent changes also in patients of the control group, but they were not statistically significant, P<0.1 and P<0.2 respectively. Other left ventricular geometry values (EDD, ESD, left atrial and right ventricular size) did not change significantly in the process of observation in the control group, as well as in the study one.

Table 1.3: Values dynamics of hemodynamics in patients with myocardial infarction and heart failure in the process of rehabilitation (M±m)

Value, measurement unit	The control group (n=20)		The study group (n=20)	
	Before treatment	**3 month**	**Before treatment**	**3 month**
EDV, ml	190.40±1.20	186.21±1.40	192.75±0.87	188.75±0.90
		P_1<0.05, P_2<0.05		P_1<0.05, P_2<0.05
ESV, ml	155.20±23.10	141.30±21.10	153.64±27.64	120.50±20.10
		P_1<0.05, P_2<0.2		P_1<0.05, P_2<0.05
EDD, cm	6.10±0.13	6.10±0.23	5.80±0.11	6.00±0.13
		P_1<0.02, P_2<0.02		P_1<0.02, P_2<0.02
ESD, cm	4.90±0.25	4.70±0.25	4.80±0.15	4.80±0.14
		P_1<0.05, P_2<0.05		P_1<0.05, P_2<0.05
Left ventricular posterior wall thickness, cm	1.20±0.08	1.30±0.06	1.18±0.06	1.18±0.06
		P_1>0.2, P_2>0.2		P_1>0.2, P_2>0.2
Interventricular septum thickness, cm	1.10±0.04	1.20±0.05	1.09±0.05	1.05±0.07
		P_1>0.5, P_2>0.5		P_1>0.5, P_2>0.5
SV, ml	81.34±3.10	87.30±4.30	80.85±4.00	92.40±4.00
		P_1<0.1, P_2<0.1		P_1<0.02, P_2<0.05
Left atrial size, cm	4.30±0.40	4.30±0.40	4.10±0.20	4.10±0.20
		P_1>0,5, P_2>0,5		P_1>0.5, P_2>0.5
Right ventricular size, cm	3.60±0.09	3.50±0.12	3.30±0.08	3.20±0.10
		P_1>0.5, P_2>0.5		P_1>0.5, P_2>0.5
EF, %	24.60±3.40	29.00±3.80	21.70±3.60	36.00±2.80
		P_1<0.02, P_2<0.02		P_1<0.05, P_2<0.05

Note: Probability of indices difference comparing to values: p_1 – before treatment, p_2 – in 3 month of treatment.

Improvement of left ventricular contractile capability occurred apparently due to many factors, but antifibrotic and vasodilating properties of carvedilol have the main significance [1-2-10-12]. Normalization of blood pressure, and presumably, improved coronary blood flow contribute to preserving of myocardium and its contractile function, as well as speeds up the regeneration process in parts of demarcation area around necrosis.

Guidelines of European Society of Cardiology on AH proposed to calculate left ventricular mass index, relative LV wall thickness, left atrial (LA) volume index, mitral annulus speed during early diastole and E/e' index. Exactly these echocardiographic markers have independent prognostic meaning and influence risk stratification of patients. This is why, on the third month of the treatment, the patients were proposed stress echocardiography method with evaluation E/e' to evaluate the decrease risk of regional coronary blood flow that is accompanied by decreased myocardial contractility.

On the basis of our observation of patients with myocardial infarction during 3 months in the rehabilitation period, it is possible to conclude that there are medications which help.

After collection of complaints, laboratory and instrumental

examinations, we observed significant metabolic changes and impaired local contractility, global LV dysfunction and pain syndrome occurred due to acute hypoxia by MI, these signs decreased significantly carvedilol use by these patients.

After echocardiography all patients underwent submaximal stress test on T2100 treadmill using Cardio soft 6.0 system (General Electric, USA) according to standard Bruce protocol. During the test, constant ECG monitoring was conducted with registration in 12 leads in order to detect ST dynamics, as well as rhythm and conduction disorders. BP was registered at the start and at the end of each stress stage, as well as in the rehabilitation period (at 1st and 5th minute). Stress test was finished when a patient reached 85% of maximal heart rate calculated according to the age or presented other standard criteria for terminating. Physical exercise tolerance was evaluated in metabolic equivalents (MET). Outright after terminating of physical exercise, the patients were returned to horizontal position on the left side and E/e' equation was evaluated (Table 1.4).

Table 1.4: Patients' hemodynamic indices by stress echocardiography

	The control group	**The study group**	
	E/e' ≥ 13 (n = 20)	**E/e' < 13 (n = 20)**	**p**
EDD, cm	5.27 ± 0.66	5.19 ± 0.26	0.67
Left ventricular mass index, g/m^2	157 (149 – 212)	149 (101 – 1498)	0.000001
Ejection fraction, %	25.00 ± 3.80	33.00 ± 2.80	0.0008
E, m/sec	0.58 (0.5 – 0.7)	0.59 (0.5 – 0.69)	0.82
e', cm/sec	5.8 (5.1 – 7)	7,8 (6.2 – 9.7)	0.0005
E/e' at rest	8.61 (7.61 – 12.65)	6.55 (5.63 – 7.67)	0.0001
Heart rate at rest, bpm	74 (62 – 83)	75 (67 – 82)	0.95

Note: p1–2 is statistical differential significance between the 1st and the 2nd groups;

The patients with increased E/e' value demonstrated after the stress test lower tolerance to physical exercise according to MET index, and the whole test duration did not exceed first two stages of Bruce protocol.

E/e' value at rest in the range from 8 to 13 may correspond to normal, as well as increased LV pressure. Value E/e' > 13 is considered as pathologic, E/e' > 14,5 after stress echo on a lying ergometer is an independent predictor of the poor diagnosis [4-5-6].

Improved myocardial contractile capability caused naturally improved physical work capability in patients that had taken carvedilol.

So, prognosis evaluation and risk stratification in patients with past myocardial infarction with the help of stress echocardiography showed that the patients in the study group, who had taken carvedilol, were more stress-resistant and had much better prognostic values in treatment.

Conclusions

1. Carvedilol even in a relatively short treatment period (3 months) causes improvement of left ventricular contractile capability, and this leads to significantly faster clinical symptomatic reduction in such patients, fastening of rehabilitation period.
2. After stress echocardiography, it is possible to speak clearly that the patients, which had received carvedilol, are more prepared to life stressed situations and have higher tolerance to physical exercises comparing to the control group.

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