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THE EFFICACY OF IVABRADINE IN IMPROVING THE CONTRACTILITY OF HIBERNATING MYOCARDIUM IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Abstract

This study focused on the dynamics of global echocardiographic indicators as well as ejection fraction and index of left ventricle regional myocardium contractility in patients with unstable angina and post-infarction cardiosclerosis during treatment with ivabradine. The study involved 59 patients, 27 of which had viable (hibernating) and 32 non-viable myocardium. The criterion for myocardial viability was defined as left ventricle ejection fraction improvement of ≥ 5% between the first and 14 day of hospitalization. Depending on the administration of ivabradine 5 mg twice a day, which began on the 2nd and 3rd day of hospitalization, patients in each group were divided into two sub-groups: A and B. The patients of subgroups I A and II A received additional ivabradine along with standard therapy, and in the subgroup I B and II B patients did not receive this drug.

Repeated echocardiography showed significant improvement in the parameters of subgroup I A. Left ventricle end systolic diameter and end systolic volume decreased by about 12%, stroke volume increased by 18.5%. Left ventricle ejection fraction in subjects with viable myocardium, especially those treated with ivabradine (I A), increased by 22.56% compared to 15.25% in the subjects not treated with the drug (I B). Analysis of the left ventricle regional myocardial contractility dynamics show significant improvement in the I A subgroup parameters – degree of local contractility decreased by 23.31% and wall motion score index by 16.77% in subgroup IA.

The subjects with non-viable myocardium (subgroups II A and II B) did not exhibit statistically significant positive changes in dimensions, volumes and left ventricle ejection fraction. Low tendency of improved standard echocardiographic parameters was observed in ivabradine-treated subjects (subgroup II A). In the same subgroup significant decrease was observed both in the degree of local contractility by 9.70% and wall motion score index by 8.84%. Opposite data obtained in subgroup II B showed a significant increase in the degree of local contractility by 13.7% and in the wall motion score index by 14.52%, which indicates enlargement of the non-viable myocardial area without treatment with ivabradine. Addition of 10 mg/day of ivabradine to standard therapy in acute coronary syndrome significantly improves global and regional left ventricle myocardial contractility, especially in patients with viable myocardium.

Keywords: *unstable angina, hibernation, wall motion score index, ivabradine.*

Introduction

Despite advances in the prevention and treatment of coronary heart disease (CHD), there is still a number of unresolved challenges related to the conservation of the structure and function of the myocardium in acute coronary syndrome (ACS) patients. Of particular importance is the study of new pathogenetic mechanisms of ischemic heart disease, the so-called "new ischemic syndromes": myocardial hibernation, "stunning" and preconditioning [*Paolo G et al., 2008; Nagel E, Schuster A, 2010; 2012*]. Formation of morpho-

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functional changes in the myocardium and their clinical manifestations is associated with impaired intracellular energy metabolism, caused by cardiomyocyte hypoxia due to a decrease in coronary blood flow which leads to left ventricular (LV) systolic dysfunction.

A detailed study of left ventricle (LV) dysfunction and identification of areas of hibernation was performed using modern imaging techniques, not readily available in general clinical practice, like positron emission tomography, myocardial scintigraphy with thallium 201, stress-echocardiography with dobutamine and contrast echocardiography. One of the most widespread imaging methods is the two-dimensional echocardiography, which allows for calculation of end-systolic dimension (ESD), end-systolic volume (ESV), stroke volume (SV) and ejection fraction (EF) of LV. The standard echocardiogram gives us the opportunity not only to determine general myocardial function, but also, with the help of local contractility index calculations, to study the degree of regional myocardial dysfunction in dynamic observations. This essentially allows for expansion of its diagnostic capabilities [*Chngryan G, Solomenchuk T, 2014*] to identify viable (hibernating) myocardium in real clinical practice.

A practical problem is the choice of therapy that preserves, as much as possible, the structure and function of the myocardium in patients with chronic and acute forms of CHD. Commonly used therapy that improve LV contractile function include revascularization procedures and standard pharmacotherapy using nitrates, β-blockers, ACE inhibitors, statins, antiaggregants, metabolic agents with cardioprotective effect, etc. [*Hamm CW et al., 2011; Montalescot G et al., 2013*].

In recent years, there is clear evidence of the efficacy of ivabradine in improving the contractility of the left ventricular myocardium in patients not only with stable CHD, but also with ACS. The randomized RIVIERA trial, conducted in ACS patients with non-ST segment elevation (n=1270), showed an improvement of cardiovascular prognosis in patients receiving ivabradine: a reduction in the number and duration of angina attacks, frequency of myocardial infarction (MI) and cardiovascular mortality risk [*Steg PG et al., 2013*]. In the experimental studies by Heusch G. et al (2008) in animals with ACS, ivabradine increased their LV EF, improved regional myocardial contractility, and reduced infarct size. Similar results were obtained in a clinical trial by Rajagobal J. et al (2010) in which administration of ivabradine in acute MI resulted in a reduction of ischemic events and the rate of adverse complications of ACS during hospitalization. Heusch G. et al (2008) also demonstrated some pleiotropic effects of ivabradine, in particular, the ability to reduce manifestations of atherosclerosis in the vascular wall, as well as improving the course of MI due to reduced necrotic zones and improved systolic function of LV. The work of Derevyanny E. et al (2013) confirmed the properties of ivabradine used in the early stages of ACS in patients with hypotension by reducing the number of ischemic events, as noted in clinical observations and Holter ECG monitoring.

To objective of this study was to determine the dynamics of the main echocardiographic indices of global and segmental contractility of the LV myocardium in ACS patients with a viable and non-viable myocardium during treatment with ivabradine.

Materials and Methods

The study involved 59 patients with unstable angina and post-infarction cardiosclerosis. Patients were randomized into 2 groups: Group I – 27 patients with viable (hibernated) myocardium (mean age 61.94 ± 2.39, 70.37% male, 29.62% female); Group II – 32 patients with non-viable (non-hibernated) myocardium (mean age 63.09 ± 2.24, 71.87% male, 28.13% female). The criterion for myocardial viability was defined as LV EF improvement of ≥ 5% between the first and 14 day of hospitalization.

Echocardiography was performed on the first and 14th day of hospitalization using an Acuson Cypress Siemens (USA) system with 3 *Mhz* frequency sectoral sensor. We studied the dynamics of basic LV echocardiographic parameters: ESD, ESV, SV and EF. Additionally, we calculated the indices of regional LV myocardial contractility: wall motion score index (WMSI) and the degree of local contractility (DLC). WMSI was derived as the sum of the wall motion scores by number of visualized segments (16), DLC was derived as total score segments: 16 / number of segments with impaired contractility [*Lebeau R et al., 2012, Chngryan G, Solomenchuk T, 2014*].

Depending on the ivabradine administration, started from the second or third day of hospitalization at a dose of 5 *mg* twice a day, patients in each group were divided into two sub-groups: A and B. Patients in subgroups I A (n=12) and II A (n=15) received additional ivabradine along with standard therapy, and patients in subgroups I B (n=17) and II B (n=15) only received standard therapy. The study excluded patients with contraindications to ivabradine.

The research data were processed on a personal computer using Microsoft Office Excel 2007 and StatSoft Statistica 6.0 programs. To assess significant differences we used Student's and Fisher test. Significance criteria was defined as $p<0.05$.

Results and Discussion

Another echocardiographic examination, performed at the end of the study, showed a significant improvement in the ESD, ESV, SV, LV EF in patients with viable (hibernating) myocardium in the subgroup treated with ivabradine (IA), compared to patients who did not receive this drug (IB) (table 1). In subgroup I A there was a decrease in ESD and ESV by about 12% (from 4.62 ± 0.13 *cm* to 4.07 ± 0.13 *cm* ($p<0.05$) and from 87.38 ± 6.88 *ml* to 76.97 ± 6.13 *ml* ($p<0.05$) respectively). In patients with myocardial hibernation not treated with I_f channel inhibitors (subgroup IB) some improvement was observed, albeit much less pronounced. In particular, the ESD only decreased by 2.6% (from 4.68 ± 0.14 *cm* to 4.56 ± 0.14 *cm*, $p<0.05$) and ESV by 8.5% (from 96.71 ± 6.35 *ml* to 88.48 ± 5.78 *ml*, $p<0.05$). The growth of SV was also observed in both groups, but with a significant prevalence in individuals who received ivabradine. In particular, the SV in the I A subgroup increased by 18.5% (from 60.11 ± 4.8 *ml* to 73.82 ± 5.28 *ml*, $p<0.05$) and in I B by 13.9% (from 54.33 ± 2.40 *ml* to 63.10 ± 2.56 *ml*, $p<0.05$). Both subgroups exhibited improved global systolic function, but with a noticeable advantage in the I A subgroup. LV EF increased among patients in subgroup I A by 22.56 % (from 38.32 ± 1.68 % to 49.48 ± 1.49 %, $p<0.05$) as compared to the I B subgroup patients by 15.25 % (from 36.48 ± 1.27 % to 43.04 ± 1.18%, $p<0.05$). Reliable increase in LV EF in Q-MI patients in patients receiving ivabradine was also recorded in the observations of Prof. Parkhomenko AN et al. (2012).

Additional analysis of the dynamics of LV regional myocardial contractility showed the same perceptible improvement in the I A subgroup as compared to IB. In particular, DLC decreased in subgroup I A by 23.31% (from 1.33 ± 0.09 to 1.02 ± 0.17, $p<0.001$), while in subgroup I B by 2.82% (from 1.42 ± 0.11 to 1.38 ± 0.09, $p<0.05$). A similar change was observed in the analysis of the WMSI. In I A subgroup of patients, the WMSI decreased by 16.77% (from 1.67 ± 0.06 to 1.39 ± 0.05, $p<0.001$) whilst in the subgroup I B – by 8.48% (1.77 ± 0.08 to 1.62 ± 0.07, $p<0.001$). The data obtained can be explained by the properties of ivabradine that sig-

Table 1

Metric, volume indicators and indicators of regional LV contractility in patients with unstable angina, against the background of myocardial infarction cardiosclerosis (M ± m)

Indicators	Patients with myocardial hibernation			
	I A subgroup (n=15)		I B subgroup (n=12)	
	1st day	14th day	1st day	14th day
ESD (*cm*)	4.62 ± 0.13	4.07 ± 0.13*	4.68 ± 0.14	4.56 ± 0.14*
ESV(*cm*)	87.38 ± 6.88	76.97 ± 6.13*	96.71 ± 6.35	88.48 ± 5.78*
SV (*ml*)	60.11 ± 4.8	73.82 ± 5.28*	54.33 ± 2.40	63.10 ± 2.56*
EF (%)	38.32 ± 1.68	49.48 ± 1.49*	36.48 ± 1.27	43.04 ± 1.18*
DLC (units)	1.33 ± 0.09	1.02 ± 0.17**	1.42 ± 0.11	1.38 ± 0.09*
WMSI (points)	1.67 ± 0.06	1.39 ± 0.05**	1.77 ± 0.08	1.62 ± 0.06**

Notes: Significant differences in the groups in the dynamics of observation * $p < 0.05$, ** $p < 0.001$.

nificantly improve the ability of LV regional contractility, especially in the presence of viable (hibernating) myocardium. The positive effect of this drug in ACS was also confirmed in other studies [*Dominguez-Rodriguez A et al., 2009; Bonow RO et al., 2011; Gerber BL et al., 2012*].

At the same time, we did not observe significant positive changes of the LV size and volume in patients with non-viable myocardium (subgroup II A and II B), although those taking ivabradine still showed low tendency of improved standard echocardiographic parameters (II A subgroup) (Table 2). In particular, the ESD and ESV have slightly decreased, from 4.27 ± 0.19 *cm* to 4.25 ± 0.15 *cm* (p>0.05) and 85.21 ± 8.18 *ml* to 82.85 ± 7.00 *ml* (p>0.05) respectively, and SV increased slightly (from 55.14 ± 3.51 *ml* and 57.57 ± 4.04 *ml*, p>0.05). In other words, preservation of the main indicators of LV contractility was observed. In the subgroup with non-hibernating (non-viable) myocardium, in the absence of treatment with ivabradine (II B), a tendency towards deterioration of ESD (from 4.30 ± 0.16 *cm* to 4.31 ± 0.15 *cm*, p> 0.05), ESV (from 87.08 ± 7.71 *ml* to 87.32 ± 7.40 *ml*, p>0.05) and SV (from 70.40 ± 3.29 *ml* to 69.40 ± 3.05 *ml*, p>0.05) was found.

Multidirectional changes in the indicators of global LV contractility were found in the subgroups II A and II B: ejection fraction in patients who received ivabradine (II A), showed a tendency to some improvement (about 2% of 40.03 ± 2.62% to 40.83 ± 2.38%, p>0.05), while in subgroup II B regression was observed (from 39.24 ± 2.03% to 38.87 ± 1.22%, p>0.05). Such changes in LV EF in patients of the group II are explained primarily by the presence of predominantly non-viable myocardium, which accounts for dominant degenerative changes near the infarction areas, and there are no reserve capabilities to restore the myocardium and its contractility. At the same time, the observed minimal tendency to positive changes in the subgroup II A, i.e. among the patients receiving ivabradine, is evidence of its properties maintaining and preserving LV function, preventing the deterioration of the global contractility of LV due to its lusitropic effect resulting in improved circulation in small coronary arteries [*Sulfi S, Timmis AD, 2006*]. Analysis of the calculated index of regional contractility in the two subgroups of patients with the non-viable myocardium (II A and II B) confirmed the above data. In the subgroup II A, significant decrease in DLC was observed by 9.70% (from 1.65 ± 0.18 to 1.49 ± 0.14, p<0.001) and WMSI by 8.84% (from 1.81 ± 0.19 to 1.65 ± 0.13, p<0.001). The opposite results were obtained in the subgroup II B, in which a significant increase of DLC by 13.7% (from 1.45 ± 0.13 to 1.68 ± 0.11, p<0.05) and WMSI by 14.52% (from 1.59 ± 0.15 points to 1.86 ± 0.12 points, p<0.05) was observed. This indicates an increase in the area of non-viable myocardium in the absence of ivabradine treatment.

Thus, prescribing ivabradine in ACS patients (in the absence of contraindications) contributes to a

Table 2.

Metric, volume indicators and indicators of regional LV contractility in patients with unstable angina, against the background of myocardial infarction cardiosclerosis (M ± m)

	Patients with non-myocardial hibernation			
	IIA subgroup (n=17)		IIB subgroup (n=15)	
Indicators	1st day	14th day	1st day	14th day
ESD, (*cm*)	4.27 ± 0.19	4.25 ± 0.15***	4.30 ± 0.16	4.31 ± 0.15***
ESV, (*cm*)	85.21 ± 8.18	82.85 ± 7.00***	87.08 ± 7.71	87.32 ± 7.40***
SV, (*ml*)	55.14 ± 3.51	57.57 ± 4.04***	70.40 ± 3.29	69.40 ± 3.05***
EF, (%)	40.03 ± 2.69	40.83 ± 2.38***	39.24 ± 2.03	38.87 ± 1.29***
DLC, (units)	1.65 ± 0.18	1.49 ± 0.14**	1.45 ± 0.13	1.68 ± 0.11*
WMSI, (points)	1.81 ± 0.19	1.65 ± 0.13**	1.59 ± 0.15	1.86 ± 0.12*

Notes: *Significant differences in the groups in the dynamics of observation: * p < 0.05; ** p < 0.001; *** p>0.05.*

more intensive restoration or preservation of systolic function and regional contractility in patients with left ventricular ACS, which is confirmed by a number of domestic and foreign studies [*Heusch G, 2008; Dominguez-Rodriguez A et al., 2009; Rajagopal J, 2010; Parkhomenko AN et al., 2012*]. The most significant improvement in LV contractile function was observed in patients with LV myocardium in a state of hibernation (IA). In addition, introduction of ivabradine induces preservation of global and regional LV myocardial contractility in ACS patients, even in patients with non-viable myocardium (II A). Many publications show positive effects of ivabradine in ACS patients. For example, in the VIVIFY randomized trial, among patients with ACS ST-segment elevation, intravenous administration of ivabradine led to the positive dynamics of all echocardiographic parameters, which characterize the LV function [*Steg PG et al., 2013*].

Conclusions

Thus, addition of 10 *mg* of ivabradine to standard therapy in ACS significantly improves global and regional LV myocardial contractility, especially in patients with myocardial hibernation.

In patients with non-viable myocardium ivabradine contributes to maintaining regional myocardial contractility. In the absence of treatment with ivabradine, these patients showed a tendency to decreasing LV EF and poorer LV regional contractility.

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