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OPTIONS FOR USING CELLULAR CARDIOMYOPLASTY FOR CORONARY HEART DISEASE

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Background. *Despite a significant arsenal of medications and methods of surgical correction of myocardial blood supply, treatment of some forms of coronary heart disease remains relevant.* ***Aim*** *of the work is to analyze the effectiveness of the use of mesenchymal stem cells (MSC) of bone marrow in autologous transendocardial transplantation in some forms of IHD.* ***Methods.*** *In the near and long-term results, we analyzed the histories and diseases and conducted a survey of 68 patients. Of the 68 patients, the largest group was men — 53 (77.9%), women were much fewer — 15 (22.1%). Then we formed 4 groups (17 patients each): 1 group — control — patients received standard drug therapy; Group 2 — to patients who received standard therapy, empty myocardial injections were performed using a catheter and the NOGA XP navigation system; Group 3 — auto-CCK was administered intravenously to patients; 4 group — against the background of therapy, transendocardial auto-MSC was administered.* ***Results.*** *When analyzing the patient's subjective sensations in group I, after 3 months in group 1, 4 patients (32%) noted improvement, unchanged — 11 (64.7%), worsening — 2 (11.8%) and significant worsening 1 (5.9%). In group 2, improvement was in 1 patient, which was 5.9%, unchanged — 13 (76.5%), worsening — 2 (11.8%) and significant deterioration — 2 (11.8%). In group 3, improvement was observed in 5 patients — 29.4%, significant improvement in 1 (5.9%), deterioration and significant deterioration in 1 patient (5.9% each, respectively). In group 4 unchanged — 6 (35.3%) patients, improvement — 7 (41.2%), significant improvement — 4 (32%), worsening — 1 (5.9%). Cell transplantation, regardless of the method of administration, increases the EF and reduces the EDV of the left ventricle, more significantly in the group with a transendocardial route of administration.* ***Conclusion.*** *In accordance with published data, we obtained similar data — transplantation of human bone marrow SSC with autologous administration causes a positive effect in the form of increased EF LV, decreased EDV of the LV, increased exercise tolerance and a significant improvement in patients' well-being. It should be noted that intravenous and intracoronary administration of auto-MSC is less effective in the studied parameters than transendocardial introduction of cells into the myocardium.*

Keywords: *coronary heart disease, cell cardiomyoplasty, myocardial revascularization, mesenchymal stem cells.*

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BACKGROUND

Coronary heart disease occupies a leading place among the causes of disability and mortality in the population of Russia and other developed countries, being a medical and social problem of modern human life [1]. Despite significant advances in the treatment of coronary artery disease, a number of controversial and unresolved issues remain regarding cardiac revascularization in patients with a sharply reduced cardiac ejection fraction (<25%) after already performed stenting and coronary artery bypass grafting. When the options for therapeutic and surgical methods of myocardial revascularization have already exhausted their resources and the question arises about further possible treatment options, in some cases, due to the low ejection fraction of the heart, it is impossible to perform reshunting surgical interventions. Another of the pathophysiological factors of coronary heart disease is damage not only to the great vessels of the heart, but also to the vessels of the microvasculature, the vessels of the epicardium, etc. [2], and only a complex effect on all links will effectively restore the blood supply to the myocardium.

One of the options for alternative therapy for patients with heart failure is mesenchymal stromal cell (MSC) transplantation [3-9]. The literature describes various methods of delivery of a cell graft: intravenous or intra-arterial (systemic administration), directly into the

coronary vessels, epicardial injections, and transendocardial graft administration [3–7]. In the scientific literature, there are conflicting data on the effectiveness of MSCs with various methods of administration. Thus, according to studies from 19 centers in North America [7], in which, in a phase II clinical study, the effectiveness of intramyocardial administration of MSCs and a cryoprotective solution in patients with heart failure was compared after 6 months. no differences were found. Other studies [8] demonstrate the efficacy of MSC transplantation in patients with heart failure and recommend cell transplantation in complex treatment in patients awaiting heart transplantation, although the authors note that different treatment regimens and methods of combination therapy do not allow a multicenter final analysis.

There is a large number of works devoted to the use of devices for prosthetic function of the left ventricle and stem cell transplantation in heart failure [9–12]. Both methods of treating heart failure have a beneficial effect on slowing myocardial hypertrophy by improving metabolism and eliminating microvascular dysfunction, while both lead to a profibrotic effect and a decrease in extracellular matrix fibrosis [10, 11]. On the other hand, mechanical unloading of the damaged myocardium reduces the rate of stem cell depletion after intramyocardial delivery by reducing the stress of the left ventricular wall, improving myocardial perfusion, and creating a more favorable microenvironment in the damaged myocardium due to a decrease in the inflammatory response in it [12].

In a number of studies, the effectiveness and safety of the use of intracoronary administration of MSCs in acute myocardial infarction have been proved [13-16]. A decrease in akinetic zones and an increase in ejection fraction were proven using single-photon emission computed tomography and echocardiography at 4 and 12 months after administration [17]. The greatest advantages were noted with transendocardial introduction of a cell graft using the NOGA XP navigation system and according to the data of preliminary electromechanical cardiac mapping CARTO XP [4, 18–20]. The symbiosis of these two techniques makes it possible to identify ischemic zones and locally introduce the graft in order to optimize angiogenesis in them. It is discussed that it is more effective to inject mesenchymal stem cells, hematopoietic stem cells, cardiomyocytes, myocytes, etc. [4, 21]. H. Burkhart et al. [22] reported on the successful use of autologous stem cells with intramyocardial administration in patients with left ventricular hypoplasia syndrome.

Today, MSCs are the most demanded type of stem cells for clinical use. Besides good therapeutic properties, MSCs are relatively easy to obtain and cultivate. Most often, MSCs are used as part of autologous therapy, but according to a number of indicators, allogeneic material may be more preferable (in an elderly patient or with a genetic disease) [23, 24]

The very first area of clinical application of MSCs, like hematopoietic stem cells, was associated with the treatment of the consequences of radioactive damage [23]. At the present stage, not only are being developed, but already successfully applied, methods of clinical therapy using MSCs in a number of areas. Among the most successful approaches, the following should be noted: correction of bone tissue diseases (reduction of clinical symptoms of osteopsatirosis, treatment of large bone defects), treatment of type 2 diabetes mellitus and heart failure, immunomodulatory therapy of autoimmune diseases (Crohn's disease, multiple sclerosis, rheumatoid arthritis) and graft versus host reactions. The positive results of the use of MSCs in the restoration of ischemic tissue, such as after myocardial infarction, ischemic stroke, acute ischemia of the lower extremities, etc., are most likely associated with the paracrine function of vascularizing factors secreted by MSCs, the most important of which is vascular endothelial growth factor (vascular endothelial growth factor, VEGF) [24, 25]. The main advantage of autologous MSC transplantation is immunological compatibility; The disadvantages are as follows: autologous MSCs (auto MSCs) are suitable for only one patient; most often, MSC therapy is performed in the elderly, and MSCs in elderly people have a lower ability to proliferate and differentiate than MSCs in young people; if the cause of the disease is of a genetic nature, then MSCs will carry the same defect; in certain diseases and therapeutic procedures, intrinsic MSCs may have a lower therapeutic potential [23]. With age, the number of MSCs in the bone marrow decreases, which requires their expansion in vitro. Long-term cultivation of MSCs leads to aging of cells, deterioration of differentiation mechanisms and other disorders [26], which leads to a decrease in the quality of the obtained cell graft.

There is evidence of tissue-engineered constructs from heart stem cells and mesenchymal cells of adipose tissue used to stimulate myocardial regeneration [17].

The aim of this work is to analyze the effectiveness of the use of bone marrow MSCs in autologous transendocardial transplantation in some forms of coronary heart disease.

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METHODS

Study design

By the method of randomized controlled random distribution, the patients were divided into 4 groups (17 patients each): Group 1 (control): patients received standard drug therapy; Group 2: patients who received standard therapy underwent empty myocardial injections using a catheter and a NOGA XP navigation system; Group 3: patients were injected intravenously with autoMSCs against the background of ongoing drug therapy; Group 4: during therapy, autologous MSCs were injected transendocardially.

Eligibility criteria

Patients included in the study received drugs that correct dyslipidemia as well as beta-blockers, calcium channel blockers, nitrates and others in combination according to selected schemes and doses. In most cases, patients have had a previous myocardial infarction (Table 1). Diabetes mellitus type 2 suffered from 39 (57.4%), obesity 27 (39.7%), atherosclerosis of the brachiocephalic vessels 52 (76.5%), atherosclerosis of the vessels of the lower extremities 14 (20.6%), arterial hypertension II–III stage 41 (60.3%), thrombophlebitis of the veins of the lower extremities in 12 (17.6%) patients. Closure of shunts and stents was observed in 52 (76.5%) patients, distal vascular lesions — in 39 (57.4%) patients.

Conditions of conduction

In order to obtain immediate and long-term results, we analyzed the case histories and conducted a questionnaire survey of 68 patients who were inpatient treatment in the Department of Cardiac Surgery of the V.C. Gusak Institute of Emergency and Reconstructive Surgery (Donetsk).

Description of medical intervention

The ideology of “empty” injections consisted in the study of the fact that mechanical damage to myocardial tissue stimulates neoangiogenesis, and thus helped us to emphasize the role of the cell transplant in the 4th group. Intravenous administration of autoMSCs was aimed at studying the homing effect (literally, the settlement of stem cells at the site of injury), which consists in the sedimentation of the main pool of the cell graft in the ischemic part of the myocardium.

After signing informed consent, all patients underwent electromechanical catheter mapping of the left ventricle using the Noga XP system (Cordis, USA). All procedures were performed using the Prucka Engineering electrophysiological laboratory (CardioLab 6.5) (GE, USA) and the Noga XP navigation system.

The femoral artery was punctured under local anesthesia using the Seldinger method. A Nogastar mapping catheter (Biosense Webster, USA) was inserted transaortally into the left ventricular cavity through an 8 Fr introducer sheath, and the left ventricular chamber was reconstructed.

The method of building the map and its color filling are based on the principle of triangulation, when the so-called grid of triangles is initially built. The distance between the anchor points plays an important role. The reliability of the reconstructed surface and its color de-

Table 1

Baseline clinical characteristics of patients

Main parameters		Group			
		1	2	3	4
Sex	Male/female	13/4	13/4	14/3	13/4
Age. years old	46–50	2	2	2	3
	50–60	7	8	7	6
	60–74	8	7	8	8
Number of MI in history (number of patients): • 1 • 2		13 (76,5%) 7 6	15 (88,2%) 6 9	15 (88,2%) 6 9	13 (76,5%) 5 8
Development of postinfarction LV aneurysms (number of patients)		4 (23,5%)	2 (11,8%)	5 (29,4%)	7 (41,2%)
Time from the last MI. years		2,9 ± 1,5	3,6 ± 2,2	3,2 ± 3,4	2,3 ± 1,8

Note. There were no differences in the clinical characteristics of the study groups and control groups ($p > 0.05$). MI — myocardial infarction, LV — left ventricle.

crease as the distance between the nodal points increases. The electrophysiologist himself chooses the scale or threshold for filling the map with color — the higher the threshold, the less "voids", i.e. the map is the most accurate and detailed. The points are marked on sinus rhythm under conditions of stability of the catheter position, stability of the local activation time (LAT), stability of the cycle length (LS not more than 3 mm) and in the absence of ST segment elevation on the unipolar reference channel. Thus, an electroanatomical map of the left ventricle is constructed. This map view displays the geometry of the left ventricle and the sequence of electrical activation of the ventricle. Indicate anatomical landmarks such as the fibrous rings of the aortic and mitral valves. The system automatically detects the apex of the left ventricle as the farthest point from the aortic valve. If necessary, the localization of the apex is changed manually. Then the electroanatomical map is switched to the unipolar voltage and mechanical (LLS) mode. On a unipolar voltage map, myocardial segments with an adhesion amplitude below 7 mV are considered a scar. On a mechanical map (LLS), zones with an amplitude of wall movement of less than 12% of the maximum are considered a scar or insufficiently vascularized myocardium. When comparing the voltage unipolar and mechanical maps, segments of the myocardium are determined that are viable, but are in a state of ischemia, and the amplitude of contraction of which is significantly reduced. These are the zones of the so-called hibernated myocardium — they are the targets for cell therapy. The unipolar voltage map (A) allows you to identify areas with low-amplitude potentials (scar) — on the map in red. The violet zones represent a viable myocardium; high-amplitude electrical activity is recorded here. Mechanical map (B) reflects the amplitude of wall movement: red zones — poorly contracting or non-contracting segments, purple zones — well-contracting myocardium. The red zones on both types of cards may not coincide, because in the areas of the hibernated myocardium, high-amplitude electrical activity is recorded, but they contract poorly. MSC suspension was injected into these zones.

The Noga XP navigation system is designed for more accurate delivery of cells to the ischemic myocardium. The principle of the system is magnetic navigation. The system allows performing volumetric reconstruction of the left ventricle, determining the viability of the myocardium and using a special injector to inject a suspension cell preparation into the desired segment.

Upon completion of the mapping of the left ventricle, the mapping catheter was replaced with a Myostar catheter (Biosense Webster, USA) intended for intramyocardial administration of active agents. The length of the retractable needle was preliminarily adjusted using a simulator of the aortic arch (the length of the extension of the needle is 1/2 of the thickness of the myocardium). Injections of mesenchymal autologous stem cells of the bone marrow were performed into the zones of the hibernated myocardium, while injections into the apex of the mitral valve were avoided due to the high risk of perforation and in the area of recording the potentials of the His bundle due to the risk of blockade development.

In order to maximize the efficiency of injections, the tip of the catheter was positioned perpendicular to the wall of the left ventricular myocardium under the control of a navigation system and fluoroscopy. When the position of the catheter was stable, the needle was extended and the cells were injected (injection). The injection rate should not exceed 0.1 ml in 15 seconds. Usually, 8-10 injections of 0.2 ml were performed. The total number of injected cells is 5×10^7.

Bone marrow explantation was performed under aseptic conditions from the iliac crest in an amount of 20–40 ml with the addition of 625 U/ml heparin (Darnitsa, Ukraine). The bone marrow aspirate was layered on a Histopaque-1077 gradient, density 1.077 g/ml (Sigma, USA) and centrifuged for 30 min at 1500 rpm. The resulting mononuclear cells were collected and sequentially washed 3-4 times in Hanks solution (Biolot, Russia) by centrifugation at 1000 rpm for 14 min. The thus obtained suspension of bone marrow mononuclear cells was inoculated into collagen-coated culture flasks with an area of 75 cm^2 (Corning-Costar, United States) at a concentration of $2–5 \times 10^6$ cells per flask.

Cultivation of MSCs was carried out in a mixture of nutrient medium DMEM/F12, 1: 1 (Sigma, USA) with the addition of 10% fetal calf serum (Biolot, Russia), 0.75 mg / ml glutamine (Institute of Poliomyelitis and Viral Encephalitis, Russia), 2 ng/ml of the main fibroblast growth factor (Sigma, USA) and 100 U / ml of penicillin and streptomycin (Darnitsa, Ukraine), in a CO2 incubator (Jouan, France) at 37 °C and 5% CO_2 atmosphere. The medium was changed every 3–4 days of cultivation. The cultures reached the primary monolayer on the 8-11th day of cultivation, depending on the inoculation density of the primary isolated cell suspension, individual characteristics of donors, and the level of cell proliferative activity. During passaging, the cells were suspended using a mixture of trypsin / EDTA solutions (Biolot, Russia) at a ratio of 0.05: 0.02% in phosphate

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buffered saline, pH 7.4 (Sigma, United States). Passage ratio was 1: 2 or 1: 3.

Ethical review

Clinical studies were carried out with the permission of the Ethics Committee of Donetsk State Medical University and the Ministry of Health (protocol No. 4 dated 02/04/2013).

Statistical analysis

The distribution of data for normality was checked using the Shapiro – Wilk test (W), which made it possible to use it even with a small sample (n <30). To identify significant differences between the mean values of different populations of comparable groups, the methods of variation statistics were used using the Student's t-test with Bonferroni's correction for multiple comparisons with the probability of a type I error $p = 0.05$. The data were considered reliable at $p < 0.05$.

RESULTS

Subjects (participants) of the study

The case histories were analyzed and 68 patients were questioned. The group was dominated by men - 53 (77.9%); patients were between 46 and 74 years old, mean age 62.4 ± 5.3 years. Disease duration ranged from 7 to 18 years, on average 8.41 ± 3.67 years. According to the classification of the New York Heart Association (NYHA), patients with chronic heart failure were distributed as follows: FC I — 0, FC II — 9 (13%), FC III — 41 (60%), FC IV — 18 (26.5%). According to the classification of angina pectoris of the Main Military Clinical Hospital. Academician N.N. Burdenko patients were distributed as follows: 2 FC — 14 (20.6%), 3 FC — 44 (64.7%), 4 FC — 10 (14.7%). The main number of patients with angina pectoris complained of discomfort and / or pain in the chest area — 65 (95.6%), pain radiated to the left shoulder, the inner surface of the left arm or the left half of the neck in 59 (86.8%). Irradiation of pain to the epigastric region was observed in 3 (4.4%) cases, asthenic syndrome — in 63 (92.6%), palpitations in the form of tachycardia and / or rhythm disturbances — in 63 (92.6%), shortness of breath — in 62 (91.2%), splenohepatomegaly — in 39 (57.4%), peripheral edema — in 44 (64.7%).

Key study findings

For a subjective assessment of the general condition of patients, we used the SAN questionnaire (health, activity, mood). According to the points scored on the questionnaire, we evaluated the result as follows: an increase by 2 points — a significant improvement, an increase by 1 point — an improvement, no changes — no effect, a decrease by 1 point — a deterioration, a decrease by 2 points — a significant deterioration. When analyzed on time after 3 months in the 1st group, improvement was noted in 4 patients (32%), there were no changes in 11 (64.7%), deterioration was recorded in 2 (11.8%) cases, significant deterioration — in 1 (5.9%). In group 2, the corresponding results were noted in 1 (5.9%), 13 (76.5%), 2 (11.8%) and 2 (11.8%) cases. In the 3rd group, improvement was observed in 5 (29.4%) patients, significant improvement — in 1 (5.9%), deterioration and significant deterioration were observed in 1 (5.9% each) patient. In the 4th group, 6 (35.3%) patients had no changes, 7 (41.2%) showed improvement, 4 (32%) — significant improvement, 1 (5.9%) — worsening. Indicators of the SAN questionnaire 6 months after cell therapy are presented in table. 2.

When studying the dynamics of the end-diastolic volume of the left ventricle (LV EDV), which is a prog-

Table 2

Results of subjective assessment of patients' well-being 6 months after the use of autoMSC

Group	Treatment efficacy						Total
	Improvement		Without changes		Worsening		
	Abs.	%	Abs.	%	Abs.	%	
1 (control)	5	29,4	10	58,8	2	11,8	17
2 (false injection)	1	5,9	14	82,4	2	11,8	17
3 (intravenous administration of MSCs)	6	35,3	10	58,8	1	5,9	17
4 (transendocardial administration of MSCs)	11	64,7	5	29,4	1	5,9	17
Total	24	35,3	38	55,9	6	8,8	68

Note. The results of treatment of patients between groups are reliable. MSC/auto MSC — mesenchymal/autologous mesenchymal stem cells.

nostic sign of heart failure, no changes were found in groups 1 and 2. In the group of 3 patients, LV EDV after 3 months decreased from 244.1 ± 24.3 to 193.4 ± 18.9 ml, but after 6 months it did not differ from the initial data. In group 4, after 3 months, there was also a decrease in LV EDV to 194.3 ± 26.4 ml, and this tendency was observed until the end of 6 months — 200.8 ± 22.8 ml; Unfortunately, in the long term, we observed a gradual increase in EDV, which is associated with the weakening of the effect of the cell graft and the progression of the disease (Table 3).

When studying the left ventricular ejection fraction (LVEF), we see that, by analogy with EDV, there are no changes in groups 1 and 2; in group 3, LVEF after 3 months increased from 33.8 ± 3.6 to 42.8 ± 4.8%, but by 6 months of observation it decreased and did not differ from the initial indicator. In group 4, LVEF increased from 41.3 ± 3.2 to 49.3 ± 4.6% and remained at this level until the end of 6 months of observation — 48.9 ± 3.4%. In more distant terms, there was a decrease in the left ventricular EF — the effect was almost absent at 12–14 months (data not shown) (Table 4).

As an illustration of the effectiveness of cell therapy, one can cite a decrease in the zone of ischemia and electromechanical dissociation when comparing the results of mapping the left ventricular myocardium before and after treatment (Fig. 1).

DISCUSSION

More pronounced signs of the effectiveness of autoMSCs after transendocardial administration for 6 months and then by 12 months level off, allowing us to assume that in this case there is a more pronounced paracrine effect of transplanted cells, i.e. when entering the ischemic zone, they produce biologically active substances that stimulate neoangiogenesis and improve myocardial metabolism. According to another hypothesis, part of MSCs can differentiate into endothelial cells, pericytes, cardiomyocytes, etc. [15, 24–26, 31], but to test this hypothesis, it is necessary to use labeled cells, which was not part of our study.

It should be noted that the homing effect of stem cells with different administration options for myocardial infarction was demonstrated by us in previously published experimental works [3–6]. Cellular cardiomyoplasty autoMSC can be performed in all patients with refractory angina pectoris. If intracoronary or transendocardial injection of a cell graft is impossible due to severe chronic heart failure, an alternative can be the intravenous method of MSC delivery.

Cellular cardiomyoplasty can be used at the preparatory stage before coronary artery bypass surgery in patients with severe left ventricular systolic dysfunction, which will increase the ejection fraction, increase the body's adaptive capabilities, and improve the tolerance of surgery. If it is impossible to perform revascu-

Table 3

Dynamics of the end-diastolic volume of the left ventricle, ml

Group	Before administration	After 3 months	After 6 months
1 (control)	251,4 ± 28,1	248,6 ± 42,1	268,3 ± 25,6
2 (false injection)	246,6 ± 22,8	210,1 ± 33,4	212,3 ± 34,7
3 (intravenous administration of MSCs)	244,1 ± 24,3	193,4 ± 18,9*	204,3 ± 45,6
4 (transendocardial administration of MSCs)	248,5 ± 22,3	194,3 ± 26,4***	200,8 ± 22,8***

Note. * — reliability of differences between the initial indicators and after 3 months; ** — reliability between the initial indicators and after 6 months; *** — significant difference between groups 2 and 3. MSC — mesenchymal stem cells.

Table 4

Dynamics of the left ventricular ejection fraction (%)

Group	Before administration	After 3 months	After 6 months
1 (control)	42,4 ± 4,2	40,3 ± 3,8	36,5 ± 3,8
2 (false injection)	36,5 ± 6,1	42,2 ± 5,2	38,8 ± 4,2
3 (intravenous administration of MSCs)	33,8 ± 3,6	42,8 ± 4,8*	40,3 ± 5,1
4 (transendocardial administration of MSCs)	41,3 ± 3,2	49,3 ± 4,6*, ***	48,9 ± 3,4**, ***

Note. * — reliability of differences between the initial indicators and after 3 months; ** — reliability between the initial indicators and after 6 months; *** — significant difference between groups 2 and 4. MSC — mesenchymal stem cells.

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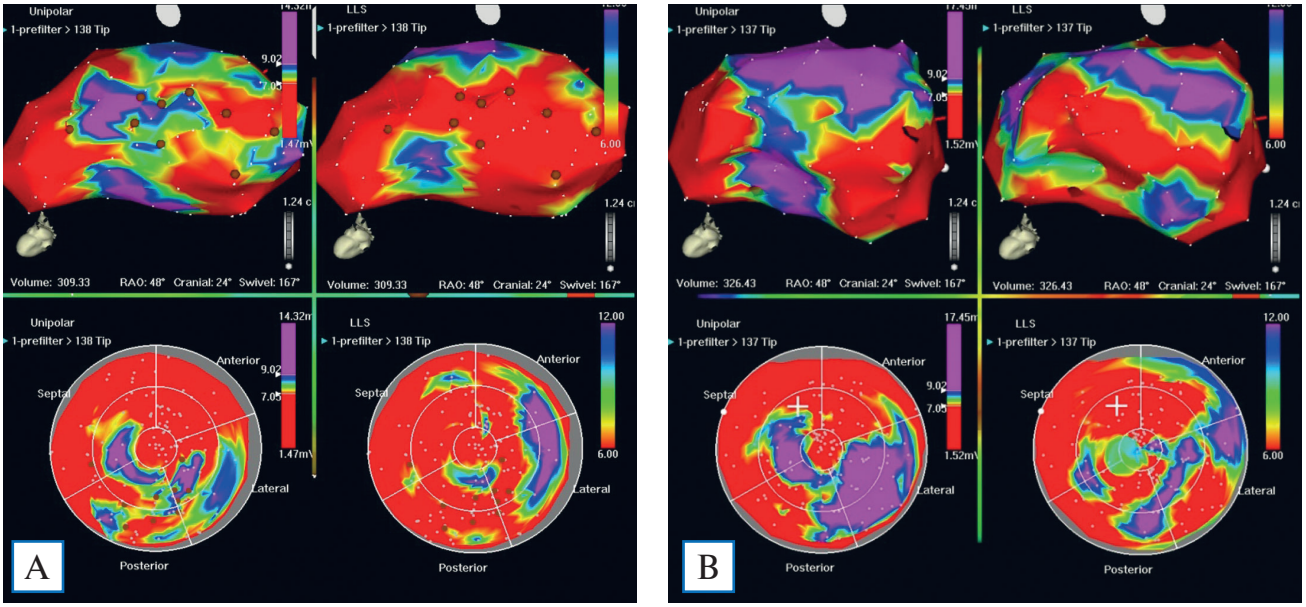
Fig. 1. Electromechanical record of patient H., 68 years old, with a diagnosis of ischemic heart disease, angina pectoris FC 4, postinfarction (Q-MI of the lower wall of the left ventricle in 2001, without Q-MI of the anterior wall of the left ventricle in 2005) and atherosclerotic cardiosclerosis; CABG-2 and MABG-1 in 2006. Shunt occlusion to the branch of the blunt edge. Stenting of the circumflex branch of the left coronary artery in 2012



Note. The left part of the figure demonstrates the electrical activity of the myocardium, the right one — the mechanical activity. A — before transplantation, B — after transplantation of autologous mesenchymal stem cells. Large areas of impaired perfusion are highlighted in red. FC — functional class, Q-MI — myocardial infarction of the lower wall of the left ventricle, CABG — coronary artery bypass grafting, MABG — mammary coronary artery bypass grafting.

larising interventions (coronary artery bypass grafting and / or stenting), cellular cardiomyoplasty can be used as an alternative to surgical intervention as an addition to basic drug therapy. The method of introducing a cell graft should be determined individually, depending on the severity of the patient's condition, changes in the coronary arteries, the degree of left ventricular dysfunction, and the forthcoming revascularising intervention.

CONCLUSION

Transplantation of autologous human bone marrow MSCs leads to an increase in the left ventricular ejection fraction, a decrease in the left ventricular end-diastolic volume, an increase in exercise tolerance, and a significant improvement in patients' well-being. Intravenous administration of autoMSCs influenced the studied parameters to a lesser extent than transendocardial administration of cells into the myocardium. One of the factors in assessing the effectiveness of cell transplantation is a decrease in the zone of ischemia and electromechanical dissociation. Unfortunately, the effect of cell therapy was short-lived — after 12 months of observation, it gradually leveled off. However, it is possible to re-introduce the graft to restore the positive hemodynamic effect.

INFORMED CONSENT

A written voluntary information consent was obtained from patients for the processing of personal data.

ADDITIONAL INFORMATION

Funding source. The study had no external funding.

Competing interests. The authors declare no conflict of interest which should be reported.

AUTHOR CONTRIBUTIONS

V.Yu. Mikhailichenko — material processing and text writing; Yu.D. Kostyamin — collection and processing of material, development of the concept and design of the study; S.A. Samarin — editing, responsibility for the integrity of all parts of the article.

All authors took an active part in the execution of the work, read, made corrections and approved the final version of the article.

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