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CARDIAC SHOCK WAVE THERAPY IN THE TREATMENT OF ISCHEMIC CARDIOMYOPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Introduction. Heart failure (HF) remains one of the greatest problems today. One of the causes of HF is ischemic cardiomyopathy (ICM). The prognosis is particularly disappointing and the most difficult to treat patients with concomitant diabetes mellitus (DM) due to the effect of hyperglycemia on vessels of different caliber and damage to nerve endings.

Cardiac shock wave therapy (CSWT) is one of the most promising noninvasive means of revascularization in the area of chronic myocardial ischemia.

The aim of the study is to evaluate the effectiveness of CSWT in the complex treatment of ICM in patients with type 2 diabetes.

Materials and methods. The study was conducted at the Regional Center for Cardiac Surgery of Odesa Regional Clinical Hospital (Odesa) in 2012–2022. 100 patients with ICM and type 2 DM were randomly divided into 2 groups. Patients in the first group (n=49) received standard therapy following current protocols. The second group (n=51) of patients additionally received CSWT complementary to standard therapy. The treatment results were evaluated at the end of the CSWT course, after 6 months, 1 year, and 2 years.

Results. The additional use of CSWT in patients with ICM with diabetes mellitus, in whom standard therapy was insufficient, showed an improvement in the quality of life and adherence to treatment. CSWT improves the contractile function of the heart, as evidenced by an increase in the ejection fraction. CSWT has a direct short-term and indirect long-term effect on the coronary vessels, in particular the microcirculatory part.

Conclusions. 1. The clinical effect of CSWT in patients with ischemic cardiomyopathy and type 2 diabetes mellitus consists in improvement of LV systolic function, increase in exercise tolerance, and reduction of heart failure severity. 2. CSWT has shown high clinical efficacy and can be recommended for use in patients with ischemic cardiomyopathy on the background of type 2 diabetes mellitus.

Key words: ischemic cardiomyopathy, coronary heart disease, diabetes mellitus, cardiac shock wave therapy.

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КАРДІОЛОГІЧНА УДАРНО-ХВИЛЬОВА ТЕРАПІЯ В ЛІКУВАННІ ІШЕМІЧНОЇ КАРДІОМІОПАТІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

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Мета дослідження – оцінити ефективність кардіологічної ударно-хвильової терапії (КУХТ) у комплексному лікуванні ішемічної кардіоміопатії (ІКМП) у хворих на цукровий діабет 2 типу.

Результати. Додаткове застосування КУХТ у хворих на ІКМП на тлі ЦД, у яких стандартна терапія була недостатньою, виявило покращення якості життя, прихильності до лікування, скорочувальну функцію серця, що підтверджується збільшенням ФВ та кількості метрів, які може пройти пацієнт під час тесту з 6-хвилинною ходьбою.

Висновки. 1. Клінічний ефект КУХТ у хворих на ІКМП та цукровий діабет 2 типу полягає у покращенні систолічної функції ЛШ, підвищенні толерантності до фізичного навантаження та зменшенні тяжкості серцевої недостатності.

2. КУХТ показав високу клінічну ефективність і може бути рекомендований для застосування у пацієнтів з ІКМП на фоні ЦД 2 типу.

Ключові слова: ішемічна кардіоміопатія, ішемічна хвороба серця, цукровий діабет, кардіологічна ударно-хвильова терапія.

Introduction

Ischemic cardiomyopathy (ICM) is the most common cause of heart failure (HF) in developed countries, with significant morbidity and mortality, despite continuous improvements in the treatment of coronary heart disease [3, 9]. This pathology may occur as a result of prolonged ischemia either after a single large acute myocardial infarction (MI) or after repeated smaller MIs that cause left ventricular (LV) dysfunction and myocardial remodeling [5, 12].

One of the main clinical consequences of ICM is chronic heart failure (CHF), one of the most serious health problems in the developed world. According to scientists, more than ten million people in Western Europe, or more than 3 per cent of the population, suffer from CHF (over 300.000.000) [6].

According to national registries and epidemiologic studies in different European countries, the prevalence of CHF among the adult population ranges from 1.5 to 5.5%

and increases with age. At the same time, 10–15% of people over 70 years old have CHF [6]. According to the literature data, at least 30% of cases are caused by ICM [12]. This is especially true for patients with concomitant diabetes mellitus (DM). On the one hand, chronic uncontrolled hyperglycemia has an extremely negative effect on large-caliber vessels, leading to rapid and severe progression of atherosclerosis. Microangiopathy develops almost simultaneously, resulting in the frequent ineffectiveness of classical operations for coronary heart disease (CHD), which allow opening of large vessels but are unable to affect the microcirculation. The diabetic autonomic neuropathy, which causes, in particular, painless forms of CHD, is a great problem. The scientists are searching for different ways to help patients with chronic coronary syndrome and ineffective surgical revascularization in the past.

Cardiac shock wave therapy (CSWT) is one of the most promising non-invasive revascularization tools in the field of chronic myocardial ischemia. Experimental studies have shown that CSWT can induce shear stress on endothelial cells and trigger a complex cascade of short- and long-term responses leading to angiogenesis [7]. An immediate increase in blood flow due to local vasodilatation and formation of new capillaries in treated tissues was detected [7; 15]. The effects of CSWT on the heart have been studied in clinical trials since 1991.

The Cochrane review analyzed the effectiveness of CSWT in patients with stable angina. The 39 studies involved 1.189 patients. The largest of these studies included 111 patients. All selected studies showed significant improvement in subjective angina symptoms and/or quality of life, and most studies showed improvement in LV function and myocardial perfusion. Overall, CSWT is a promising non-invasive method for patients with severe or poorly controlled coronary artery disease, but data are limited to small samples of single-centre studies [15].

The aim of the study is to evaluate the effectiveness of CSWT in the complex treatment of ICM in patients with type 2 DM by evaluating the dynamics of structural and functional parameters of the LV, patients' tolerance to physical activity and quality of life indicators.

Material and methods

The study was conducted at the Regional Center for Cardiac Surgery of Odesa Regional Clinical Hospital (Odesa) in 2012–2022. 100 patients with ICM and type 2 DM were included in an open-label, controlled, prospective, and single-center study. The following criteria were used to diagnose ICM: decreased myocardial contractility (LVEF (left ventricular ejection fraction) ≤40% according to echocardiography) due to coronary heart disease (patients either had a history of infarcts and/or critical changes on coronary ventriculography). Inclusion criteria: men and women of 42 to 78 years old diagnosed with ICM and concomitant type 2 DM; regular use of prescribed therapy for at least 1 month before inclusion and insufficient effectiveness of drug treatment (patients had clinical signs of heart failure and reduced ejection fraction), LVEF less than 40%, confirmed coronary artery disease (history of coronary angiography). Verification of the diagnosis of ICM and type 2 DM was performed in accordance with European and North American guidelines [1; 5; 14]. Exclusion criteria: acute coronary syndrome for less than 30 days, presence of thrombi in the LV cavity, severe decompensated DM, acute heart failure, active cancer, life expectancy less than a year, alcohol or drug dependence, terminal hepatic or renal failure. All patients voluntarily signed the initial intake form No. 003-6/o "Informed voluntary consent of the patient to diagnosis, treatment, surgery and anesthesia and to the presence or participation of participants in the educational process", approved by the Order of the Ministry of Health of Ukraine No. 110 dated February 14, 2012 (as amended by the Order of the Ministry of Health of Ukraine No. 2837 dated December 09, 2020).

The patients were randomly divided into 2 groups. The patients in the first group (n=49) received standard therapy for CHD and DM according to current standards. The second group (n=51) of patients received CSWT in addition to the standard therapy. Treatment results were evaluated after the end of the CSWT course, in 6 months, 1 year and 2 years.

The study protocol was created in accordance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) for randomized trials in parallel groups [8], and the study was conducted in accordance with good clinical practice, the Declaration of Helsinki, 2013.

The technique of the procedure, indications and contraindications were in accordance with the recommended international protocol for CSWT using the Medispec Cardiospec device (Medispec Ltd., Germantown, Maryland, USA) [11]. The treatment consisted of 9 sessions, 3 sessions each at weeks 1, 5 and 9. During one procedure, 2–3 zones of hibernating myocardium were treated with 100 pulses per zone. The principle of operation of Cardiospec is electrohydraulic. A high voltage generator creates an electric discharge in a chamber filled with water. A micro-explosion then occurs underwater, producing a high-energy shock wave. The wave is reflected from the ellipsoidal surface of the chamber, passes through the rubber membrane and is focused in the target area of the myocardium (Fig. 1). Treatment does not require anesthesia [13].

Fig. 1. Cardiac shock wave therapy procedure

At the time of inclusion in the study and at visits after 3, 6, 12, 24 months of follow-up, quality of life (QOL) parameters of patients were assessed using the EQ-5D-5L questionnaire [4], adherence to treatment using the Morisky-Green questionnaire [2], NYHA functional class of heart failure, transthoracic echocardiography (TTE) with LVEF measured with the Simpson method (ESAOTE, MyLab 40 (Esaote Ltd, Maastricht, The Netherlands)), areas of hibernating myocardium were determined by stress echocardiography with dobutamine, stress echocardiography was performed in dynamics to monitor changes in the location and size of hibernating myocardial zones [10]. The mean duration of follow-up was 24 months.

Statistical analysis was performed using Statistica 13.0 (TIBCO, USA). Continuous data with normal distribution are expressed as mean ± standard deviation and were compared using paired *t*-test at baseline and follow-up. Categorical data are expressed as frequency (n) or ratio (n/N) and compared using chi-square test. Rank data were tested using non-parametric rank sum test. A value of two-sided $p<0.05$ was considered statistically significant.

Results

Both groups consisted predominantly of men. At the time of inclusion, patients in groups 1 and 2 were comparable in age, fasting glycaemia and glycated haemoglobin levels, heart rate and blood pressure (Table 1).

All patients had CHD with reduced EF at the time of inclusion, and in both groups more than half of the patients had NYHA class III. All patients had a history of coronary angiography, which revealed coronary vessel lesions ≥70%.

At the beginning of the study, patients in both clinical groups were taking several medications, usually more than 5 drugs. In most patients, all the recommended classes of prognosis-modifying drugs were represented (83% in group 1 and 85% in group 2. The distribution of drug groups received by patients is shown in Table 1).

The areas of hibernating myocardium identified by stress echocardiography with dobutamine were exposed to shock wave impulses. In group 1, the average number of myocardial hibernation zones was 1.9±0.1, in group 2 – 2.0±0.1, p=0.9.

The average follow-up period was 1.8 years.

At the beginning of treatment (at the time of inclusion in the study), the average level of treatment adherence was 3.7±0.1 and 3.6±0.1 (p=0.9) in groups 1 and 2, respectively. When assessing the level of patient compliance in both clinical groups, it was found that adherence to therapy improved over time in group 2. So, if in group 1, a year after the start of therapy, the average score was 3.1±0.3, then in group 2 it was 2.2±0.2 (p =0.03). After a 2-year follow-up, treatment adherence was 2.5±0.4 in group 1 and 2.1±0.3 in group 2. This corresponded to a low level of adherence in both groups. Increased adherence to treatment in both groups is primarily due to more frequent visits to the doctor and more careful monitoring by medical staff.

According to the results of the EQ-5D-5L questionnaire, patients in group 1 rated their quality of life at 48±5 points, and patients in group 2 – 51±7 points at the time of inclusion in the study. Patients in group 1 rated their quality of life at 3 months at 55±4; 6 months at 62±5; 12 months at 58±6, and 24 months at 52±4 points. Accordingly, patients in group 2 assessed the quality of life at 3 months at 59±5, 6 months at 75±3, 12 months at 68±4 and 24 months at 60±7 points (Fig. 2).

Table 1

Comparison of clinical characteristics of patients in groups 1 and 2 at the time of inclusion

Parameter	Group 1 (n=49)	Group 2 (n=51)	p
Gender, % men/women	84.1/15.9	86.3/13.7	0.50
Age, years	62±6.8	62.5±5.5	0.11
Fasting blood glucose, mmol/l	7.4±1.2	7.7±1.3	0.15
$HbA1_c$, %	7.8±1.1	8.2±1.2	0.10
Heart failure II FC, % III FC, % IV FC, %	 34.5 56.8 8.7	 28.2 63.5 8.3	 0.08 0.25 0.13
LVEF, %	34.4±4.6	35.2±3.2	0.22
Heart rate, beats/min	84.3±11.3	85.6±13.1	0.40
Systolic BP, mm Hg	131.9±17.8	128.5±17	0.27
Diastolic BP, mm Hg	79.5±13.5	75.5±9.0	0.08
Drug therapy, % of patients – angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers – beta blockers – mineralocorticoid receptor antagonist – sodium-glucose co-transporter 2 inhibitors – diuretics – antiplatelet drugs – statins	 80 71 41 29 94 86 71	 85 63 47 25 96 88 73	 0.38 0.08 0.14 0.33 0.16 0.09 0.08

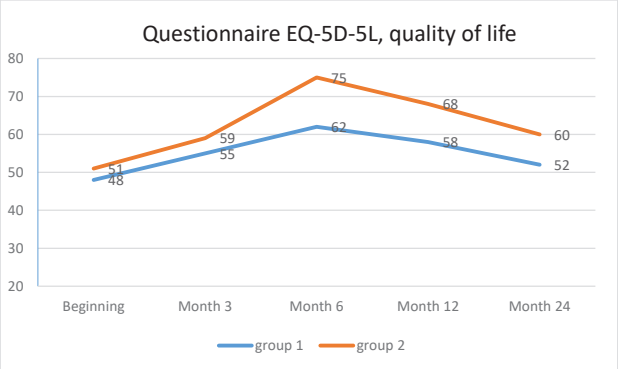
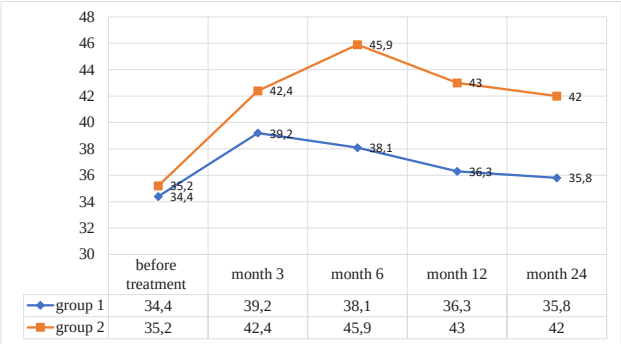


Fig. 2. Comparison of the quality of life in the groups

The dynamics of changes in LVEF during follow-up is shown in Figure 3. The addition of CSWT to the standard therapy of patients with ICM and concomitant type 2 DM leads to improvement in LV systolic function. Both groups showed an increase in EF compared with baseline (group 1 – (34.4±4.6)%, group 2 – (35.2±3.2)%, but in group 2 the changes were more pronounced. From 3 months onwards, some differences were observed between the groups. By the third month of follow-up they were insignificant (group 1 – (39.2±1.1)%, group 2 – (42.4±2.2)%), but pronounced – by the sixth month (group 1 – (38.1±1.8)%,

group 2 – (45.9±2.1)%). After 12 months of the follow up, statistically significant differences between the groups persisted (group 1 – (36.3±2.2)%, group 2 – (43.0±3.1)%). After 24 months, LVEF almost returned to baseline in group 1 (35.8±0.7)%. In group 2, LVEF gradually decreased, but remained statistically higher than the baseline (42±0.7)% (Fig. 3). Positive changes in LVEF in group 2 indicate the compliance of the applied dose load with CSWT.



	before treatment	month 3	month 6	month 12	month 24
group 1	34,4	39,2	38,1	36,3	35,8
group 2	35,2	42,4	45,9	43	42

Fig. 3. Dynamics of LVEF in clinical groups

Discussion of the results

At the time of inclusion in the study, standard drug therapy was poorly effective in all patients, which allowed us to randomize patients into groups. The additional use of CSWT in patients with ICM and DM, in whom standard therapy was insufficient, showed an improvement in the quality of life and adherence to treatment. Improved adherence to treatment, in turn, improved the course of ICM, most likely due to frequent visits to the doctor, greater control and motivation. Improved quality of life also encouraged patients to pay more attention to therapy. CSWT has a positive effect on the quality of life of patients with ICM and type 2 DM, reduces patient's dependence on outside help, improves emotional state and perception of their own health.

CSWT improves the contractile function of the heart, which is confirmed by EF increase. A difference in performance was observed as early as month 3, but it was statistically insignificant. After 6 months of the study, there was a statistically significant trend between the groups (by the 6th month LVEF in group 1 was (45.9±0.7)%, in group 2 – (38.1±0.9)%, p=0.09). In 24 months, the indicators in both groups almost returned to the initial ones. However, in group 2, there was a tendency to improve EF, and quality of life even compared to the initial values. These changes may be due to the following factors: increased supervision by medical staff and CSWT effect. CSWT has a direct short-term and indirect long-term effect on coronary vessels, in particular the microcirculatory part. According to the researchers, CSWT causes a temporary dilation of the coronary arteries by stimulating NO production. In the long-term period local exposure to electromagnetic waves stimulates angiogenesis of small vessels [12]. These processes are especially relevant for patients with DM, which is characterized by a combination of macroangiopathy and microangiopathy. During the follow-up period, 8 patients in the first group and 4 patients in the second group died of MACE. The difference is not statistically significant, but we see a tendency to better survival of patients who underwent CSWT.

Considering that the maximum changes were observed 6 months after the start of CSWT procedure, and after 2 years of the study in the patients of the second group there was a tendency for all parameters to return to the baseline level, it makes sense to repeat the CSWT to achieve a better and longer effect.

Conclusions:

1. The clinical effect of CSWT in patients with ICM and type 2 DM lies in the improvement of the quality of life (assessed by the EQ5D questionnaire) and the state of myocardial contractility (as measured by an increase in EFLV).

2. There is a tendency to improve treatment adherence in both groups, which is mainly due to more frequent visits to the doctor and more careful monitoring by medical staff.

3. CSWT has shown high clinical efficacy and can be recommended for patients with ischemic cardiomyopathy and type 2 diabetes mellitus.

BIBLIOGRAPHY

1. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J.* 2023; 44(37): 3503–3626. doi: 10.1093/eurheartj/ehad194.
2. Ben AJ, Neumann CR, Mengue SS. The Brief Medication Questionnaire and Morisky-Green test to evaluate medication adherence. *Rev Saude Publica.* 2012; 46(2): 279–89. English, Portuguese. doi: 10.1590/s0034-89102012005000013.
3. Bhandari B, Quintanilla Rodriguez BS, Masood W. Ischemic Cardiomyopathy. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537301/.
4. Craig BM, Rand K. Choice Defines QALYs: A US Valuation of the EQ-5D-5L. *Med Care.* 2018; 56(6): 529–536. doi: 10.1097/MLR.0000000000000912.
5. Ebell MH. ACC/AHA Guideline for the Management of Patients with Chronic Coronary Disease. *Am Fam Physician.* 2024; 109(3): Online. PMID: 38574227.
6. Bozkurt B, Ahmad T, Alexander KM, et al. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. *Journal of Cardiac Failure*. 2023; 29(10): 1412–1451. doi: https://doi.org/10.1016/j.cardfail.2023.07.006.
7. Li H, Liu ML. Cardiac shock wave therapy: an alternative non-invasive therapy for refractory angina. *Eur Rev Med Pharmacol Sci*. 2018; 22(16): 5402–5410.
8. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomized trials. *BMJ*. 2010; 340: 869. doi: 10.1136/bmj.c869.
9. Pastena P, Frye JT, Ho C, Goldschmidt ME, Kalogeropoulos AP. Ischemic cardiomyopathy: epidemiology, pathophysiology, outcomes, and therapeutic options. *Heart Fail Rev.* 2024; 29(1): 287–299. doi: 10.1007/s10741-023-10377-4.

10. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for Performance, Interpretation, and Application of Stress Echocardiography in Ischemic Heart Disease: From the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2019; 33(1): 1–41. doi: https://doi.org/10.1016/j.echo.2019.07.001.
11. Rassweiler JJ, Knoll T, Köhrmann KU, et al. Shock wave technology and application: an update. *Eur Urol.* 2011; 59: 784–96. doi: 10.1016/j.eururo.2011.02.033.
12. Sekulic M, Zacharias M, Medalion B. Ischemic Cardiomyopathy and Heart Failure. *Circ Heart Fail*. 2019; 12(6): 006006 doi: 10.1161/CIRCHEARTFAILURE.119.006006.
13. Shkolnik E., Burneikaitė G, Jakutis G, et al. A randomized, triple-blind trial of cardiac shock-wave therapy on exercise tolerance and symptoms in patients with stable angina pectoris. *Coronary Artery Disease*. 2018; 29(7): 579–86. Available from: https://insights.ovid.com/pubmed?pmid=29912782.
14. The American Diabetes Association's (ADA's) Standards of Medical Care in Diabetes. *Diabetes Care*. 2024; 47: 158–178. doi: https://doi.org/10.2337/dc24-S009.
15. Yang P, Guo T, Wang W, et al. Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. *Heart Vessel.* 2013; 28(3): 284–91. doi: 10.1007/s00380-012-0244-7.

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