# Optimization of a Comprehensive Prehabilitation Program for Patients with Stable Coronary Artery Disease Undergoing Elective Coronary Artery Bypass Grafting

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**Aim.** To evaluate the effectiveness of a comprehensive prehabilitation program including the optimization of drug therapy for patients undergoing elective coronary artery bypass grafting (CABG).
**Material and methods.** 56 male patients with stable angina referred to elective on-pump CABG were enrolled in a study. All patients were screened for eligibility according to the inclusion/exclusion criteria and then randomized into two groups. Group 1 patients (n=28) underwent preoperative management (prehabilitation) for 14 days, including patient education and physical rehabilitation. Trimetazidine in a dose of 80 mg per day was added to the standard drug therapy. Group 2 patients (n=28) underwent similar preoperative management, but with the standard drug therapy without trimetazidine. In addition to the routine methods of preoperative management, all patients underwent the 6-minute walk test (6MWT) to assess exercise tolerance and speckle tracking echocardiography to measure left ventricular (LV) longitudinal deformation. Serum troponin T was measured in all patients. The measurements were performed at admission and after the surgery.
**Results.** Patients did not differ in the main clinical and demographic data, as well as the main preoperative speckle tracking echocardiography findings. The intraoperative parameters were comparable in both groups. The rate of early postoperative complications was 61% (n=17) in Group 1 and 64% (n=18) in Group 2 (p>0.05).
LV ejection fraction significantly decreased postoperatively in both groups (p<0.01) as well as LV longitudinal deformation as compared to the baseline. Patients receiving the standard therapy without trimetazidine reported a significant decrease in the longitudinal strain after CABG compared with the baseline (p=0.01). There were no statistically significant differences in most preoperative and postoperative indicators of longitudinal deformation among patients treated with trimetazidine. Postoperative values of GLPS-LAX and GLPS-Avg were significantly higher in the trimetazidine group than those in the control group (p=0.04).
Group 1 patients reported longer distance covered in 6MWT than Group 2 patients while assessing exercise tolerance: 370.0 [260.0;415.0] vs 242.0 [202.0;350.0] m, respectively (p=0.0059).
**Conclusion.** The addition of trimetazidine in a dose of 80 mg daily in the prehabilitation program for patients undergoing elective CABG demonstrated better postoperative indicators of LV longitudinal deformation and an increase in exercise tolerance. Obtained findings allowed considering this approach to the preoperative management as an additional method of cardiac protection and optimization of the functional status of patients

**Keywords:** coronary artery disease, coronary artery bypass grafting, cardioprotection, prehabilitation, trimetazidine.

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Coronary artery bypass grafting (CABG), while continuing to be one of the most popular methods of surgical treatment of coronary artery disease (CAD), even nowadays is accompanied by sufficiently high rate of postoperative complications [1]. Exacerbating the problem is that the existing trends regarding the "portrait" of a patient undergoing cardiac surgery include those in the older age group with a significant comorbidity [2,3]. This emphasizes the need to improve strategy for perioperative management of patients with a particular focus on organ protection. For this, it seems appropriate to use the patient's waiting period for surgery [4]. In this context, the use of prehabilitation as a set of measures for the preoperative management of patient, including training, adequate drug therapy, therapeutic and respiratory gymnastics, physical training, methods of psychoprophylaxis and psychocorrection, is becoming increasingly important. Using this strategy, the optimization of pharmacological therapy can be considered as an effective and safe way to provide organoprotection and modify the surgical risk profile.

Trimetazidine as a component of basic antianginal therapy increases cell tolerance to ischemia by switching metabolism from fatty acid oxidation to glucose oxidation. There is evidence of the protective effects of trimetazidine against ischemia-reperfusion injury by improving endothelial function and increasing coronary flow reserve [5]. This allows us to consider trimetazidine as an additional facility for providing organoprotection, including those patients in preoperative period before direct myocardial revascularization.

The aim of the study was to evaluate the effectiveness of a comprehensive prehabilitation program including the optimization of drug therapy for patients undergoing elective coronary artery bypass grafting.

## Material and methods

56 male patients with stable angina referred to hospital in preoperative period before elective on-pump CABG were enrolled in a study. All patients presented multivessel coronary artery disease with SINTAX score of 26.2 [23.7; 30.2]. The study was approved by the Local Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases, all patients provided written informed consent to participate in the study. Exclusion criteria were: age above 75 years, body mass index (BMI) >35 kg/m$^2$, concomitant atrial fibrillation, Parkinson's disease or symptoms of parkinsonism, severe hepatic impairment (10-15 Child-Pugh points), chronic renal failure with creatinine clearance less than 30 ml/min, unstable angina or myocardial infarction (MI), decompensation of chronic heart failure (CHF), left ventricular ejection fraction (LVEF) <40%, elective reconstructive interventions on extracranial and peripheral arteries or surgical correction of valvular heart defects. All patients were screened for eligibility according to the inclusion/exclusion criteria and then randomized into two groups. Patients of group 1 (n=28, mean age 66.0 [57.0;71.0] years) underwent preoperative management (prehabilitation) for 14 days, including educational programs and optimal pharmacological treatment for CAD (angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, beta-blockers, statins, acetylsalicylic acid) along with therapeutic and respiratory gymnastics and controlled walking. Trimetazidine (Preductal OD) in a dose of 80 mg daily was added to the standard drug therapy for 14 days of the preoperative period. Patients of group 2 (n=28, mean age 64,0 [59,0;66,0] years) underwent similar preoperative management, but with the standard drug therapy without trimetazidine. All patients underwent direct myocardial revascularization (on-pump CABG). In addition to the routine methods of preoperative management, all patients on admission underwent the six-minute walk test to assess exercise tolerance and speckle tracking echocardiography (ECHO) to measure left ventricular longitudinal deformation. Serum troponin T was measured in all patients.

ECHO was performed using General Electric Vivid iq equipment with 3Sc-RS multi-frequency sector phased transducer (frequency of 1.3-4.0 MHz). The following morphometric and functional parameters were estimated: cardiac chambers diameters – left atrium (LA) and ventricle (LV), end systolic and diastolic diameters of the LV (LV ESD and LV EDD), the end systolic and diastolic volumes of the LV (LV ESV and LV EDV), the thickness of the walls of the LV and interventricular septum (IVS) and LVEF according

to the Teicholz method. Global LV longitudinal deformation was assessed in two-dimensional mode from the apical position using the speckle-tracking technique with the AFI option. The following parameters were analyzed: global longitudinal peak strain (GLPS Avg), as well as LV deformation from four- (GLPS A4C), two- (GLPS A2C) and five-chamber (GLPS LAX) positions. The normative values for the global longitudinal strain were taken from -18% and less [6]. The six-minute walk test was carried out according to the standard method. The measurements were performed at baseline and on the 5-7 day after the surgery.

Quantitative assessment of the concentration of the marker of myocardial damage troponin T was performed using an immunochemical express analyzer Cardiac Reader (Roche Diagnostics, Switzerland) the day before surgery and then on the 2nd and 5-7th days of the postoperative period. A concentration of 0.1 ng/ml was taken as the threshold value.

The management of patients in the postoperative period did not differ and rehabilitation was carried out in accordance with the Russian clinical guidelines (2016) [7].

Statistical analysis was performed using the Statistica 10.0 software package (Statsoft, USA) and included the calculation of absolute values and their percentages, as well as the median and interquartile range (Me [Q25; Q75]). The distribution of the data differed from normal, therefore, the intergroup differences were assessed using nonparametric criteria: Pearson's $\chi^2$ with Yates' correction – to compare two independent groups by a qualitative characteristic, the Mann-Whitney test – to compare two independent groups by a quantitative characteristic, Wilcoxon test – to compare two dependent groups by quantity. Differences were considered statistically significant at p value $\leqslant 0.05$.

## Results

At the initial stage we analysed the main characteristics of the studied groups in the preoperative period. The study sample was dominated by patients with stable angina of functional class II (FC) – 45 (80%), hypertension – 52 (93%) and history of myocardial infarction – 36 (64%), all patients had FC II NYHA of chronic heart failure, 22 (39%) of them were smokers, 15 (27%) patients had type 2 diabetes mellitus. The average age was 64.0 [59.0; 69.0] years, patients were overweight (BMI 27.5 [24.9;31.1] kg/m$^2$) with abdominal type of obesity (waist circumference – 105.5 [100.5;114.5] cm) with preserved LVEF (63.0 [60.0;68.0]%). Comparative analysis did not reveal any statistically significant intergroup differences in clinical and historical characteristics (Table 1).

The patients of the studied groups did not differ in the medical treatment. Accordingly, 86% of patients in both groups received four-component therapy for coronary artery disease (beta-blockers, acetylsalicylic acid, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists) at the outpatient stage. During in-hospital period the patients did not present any clinical manifestations of exertional angina, in addition, none of them showed an increase in troponin T concentration before the CABG.

Patients also did not differ in the main preoperative ECHO data and indicators of LV longitudinal deformation (Table 2).

The intraoperative parameters were comparable in both groups. The total procedure duration in group 1 was 189.5 [182.0;235.0] min while in group 2 – 192.5 [160.0;210.0] min, ($p>0.05$); the time of aortic compression was 42.0 [31.0;48.0] and 38.0 [31.0;63.0] min, respectively ($p>0.05$); the duration of artificial extracorporeal circulation – 67.0 [53.0;82.0] and 64.0 [60.0;97.0] min, respectively ($p>0.05$); the number of bypass shunts – 2.0 [2.0;3.0] in both groups.

The comparative analysis showed that the studied groups did not differ in the main baseline characteristics, including the ECHO parameters, as well as intraoperative indicators.

During the postoperative period, the following clinical parameters were assessed: the presence of angina pectoris, the rate and profile of postoperative complications along with the duration of hospital stay. Among the studied groups, there was no symptoms of angina pectoris during the postoperative period. The structure of complications in the early postoperative period included predominantly hydrothorax, which did not require pleural puncture, in 12 (43%) patients in group 1 and 13 (46%) pa-

Table 1. Basic clinical and historical characteristics of patients in the preoperative period of CABG, depending on the prehabilitation program

| Parameters | Group 1 (n=28) | Group 2 (n=28) | P value |
|---|---|---|---|
| Age, years | 66.0 [57.0;71.0] | 64,0 [59,0;66,0] | >0.05 |
| BMI, kg/m$^2$ | 28.6 [23.6;31.5] | 26,5 [24,9;31,1] | >0.05 |
| Waist circumference, cm | 104.0[102.0;111.0] | 109,5[99,0;116,0] | >0.05 |
| Smoking, n (%) | 10 (36) | 12 (43) | >0.05 |
| Social status (employed), n (%) | 9 (32) | 11 (39) | >0.05 |
| EuroScore, points | 0.66 [0,60;0,74] | 0,59 [0,55;0,84] | >0.05 |
| History of CAD, years | 4.0 [2.0;10.0] | 3.0 [1.0;12.0] | >0.05 |
| Hypertension, n (%) | 24 (86) | 28 (100) | >0.05 |
| FC of stable angina, n (%): | | | |
| II | 23 (82) | 22 (78.6) | >0.05 |
| III | 5 (18) | 6 (21.4) | >0.05 |
| Chronic heart failure of II FC NYHA, n (%) | 28 (100) | 28 (100) | >0.05 |
| History of myocardial infarction, n (%) | 16 (57) | 20 (71) | >0.05 |
| History of stroke/TIA, n (%) | 1 (3) | 2 (7) | >0.05 |
| Dyslipidemia, n (%) | 8 (28,5) | 11 (39) | >0.05 |
| History of diabetes, n (%) | 8 (28,5) | 7 (25) | >0.05 |
| Six-minute walk test results, м | 357.5 [285.0;393.0] | 350.0 [270.0;425.0] | >0.05 |

Data are presented as Me [Q25;Q75], unless otherwise stated

CABG – coronary artery bypass grafting, CAD – coronary artery disease, BMI – body mass index, TIA – transient ischemic attack, FC – functional class

Table 2. Morphofunctional parameters of the heart, assessed by transthoracic echocardiographic examination in the preoperative period of CABG

| Parameters | Group 1 (n=28) | Group 2 (n=28) | P value |
|---|---|---|---|
| LVEF, % | 63.0 [52.0;68.0] | 64.0 [60.0;70.0] | >0.05 |
| LV EDV, ml | 141.0 [124.0;180.0] | 141.0 [124.0;160.0] | >0.05 |
| LV ESV, ml | 51.0 [35.0;62.0] | 51.0 [41.0;58.0] | >0.05 |
| LV EDD, cm | 5.4 [5.1;6.0] | 5.4 [5.1;5.7] | >0.05 |
| LV ESD, cm | 3.5 [3.0;4.9] | 3.5 [3.2;3.7] | >0.05 |
| LA, cm | 4.2 [3.9;4.5] | 4.2 [4.0;4.3] | >0.05 |
| IVS, cm | 1.1 [0.9;1.1] | 1.0 [1.0;1.2] | >0.05 |
| LVPW, cm | 1.0 [0.9;1.1] | 1.0 [1.0;1.2] | >0.05 |
| Systolic output, ml | 90.0 [70.0;100.0] | 90.0 [83.0;102.0] | >0.05 |
| GLPS LAX, % | -19.7 [17.4;19.9] | -18.3 [16.3;18.7] | >0.05 |
| GLPS A4C, % | -16.8 [15.9;19.2] | -18.0 [14.5;18.8] | >0.05 |
| GLPS A2C, % | -18.7 [16.4;20.3] | -19.8 [17.6;22.1] | >0.05 |
| GLPS Avg, % | -18.7 [16.4;19.9] | -18.3 [16.2;19.0] | >0.05 |

Data are presented as Me [Q25; Q75]

CABG – coronary artery bypass grafting, LV – left ventricle, LVEF – left ventricular ejection fraction, LV EDV – left ventricular end diastolic volume, LV ESV – left ventricular end systolic volume, LV EDD – left ventricular end diastolic diameter, LV ESD – left ventricular end systolic diameter, LA – left atrium, IVS interventricular septum, LVPW – left ventricular posterior wall, GLPS LAX – the indicator of global LV deformation in the longitudinal direction from the five-chamber position, GLPS A4C – the indicator of global LV deformation obtained from the four-chamber position, GLPS A2C – the indicator of global LV deformation in the longitudinal direction from the two-chamber position, GLPS Avg – the average global LV deformation in the longitudinal direction

tients in group 2. Paroxysmal atrial fibrillation represented another frequent complication, registered in 4 (14%) of patients in both groups. In addition, one patient in group 1 developed bleeding that required resternotomy. There was registered one case of pneumothorax in patient of group 2, which resolved conservatively. Consequently, the rate of early postoperative complications was 61% (n=17) in Group 1 and 64% (n=18) in Group 2 (p>0.05) without statistically significant difference.

None of the patients experienced perioperative myocardial infarction, as well as signs of significant myocardial damage, confirmed by laboratory results of the troponin T concentration, which did not exceed the threshold values for patients after CABG. There were no significant intergroup differences in this characteristic value both on the 2nd and 5-7th days after the surgery.

Evaluation of the dynamics of ECHO parameters in the postoperative period revealed a decrease in LVEF in both groups compared to preoperative values without significant intergroup differences. Thus, in group 1 (with trimetazidine) LVEF before and after CABG was 63.0 [52.0;68.0] and 54.5 [53.5;58.0]%, respectively (p<0.01); in group 2 (without trimetazidine) – 64.0 [60.0;70.0] and 56.0 [55.0;61.0]%, respectively (p<0.01). The results may reflect the typical course of the early postoperative period: the deterioration of LV contractile function after "open" heart surgery can be explained by cardioplegia and "surgical trauma".

There is evidence that the global longitudinal strain is an indicator of myocardial hypertrophy and ischemia and can be considered as a quantitative index of the global LV function [8]. Taking into account the potential significance of this parameter as an early marker of myocardial dysfunction, the next stage of the study was to assess the dynamics of LV longitudinal deformation in the studied groups. It was demonstrated that in the early postoperative period there was a deterioration in the LV longitudinal deformation parameters in both groups compared to preoperative values (Table 3).

However, it was noted that in group with preoperative trimetazidine treatment in addition to other prehabilitation measures, the deterioration of longitudinal strain after CABG was less noticeable than in group with standard drug therapy. At the same time, significantly better values of GLPS LAX and GLPS Avg indicators were registered in postoperative period in the trimetazidine group.

Assessment of the physical status of patients in the postoperative period showed significantly better results of six-minute walk test among patients received trimetazidine during preoperative preparation compared with those without trimetazidine: 370.0 [260.0;415.0] and 242.0 [202.0;350.0] m, respectively (p=0.0059).

## Discussion

Optimal drug treatment also contributes to better cardioprotection at the preoperative stage, and it is advisable to provide effective medication, modify risk factors and comorbidity [9]. There is evidence of the effectiveness of prehabilitation measures in the postoperative period: reducing the rate of complica-

**Table 3. Parameters of longitudinal left ventricular deformation before and after CABG, depending on the preoperative approach**

| Parameters | Group 1 (n=28) | | Group 2 (n=28) | |
|---|---|---|---|---|
| | Before CABG | After CABG | Before CABG | After CABG |
| GLPS LAX, % | -19.7 [17.4;19.9] | -12.0 [10.7;13.7] | -18.3 [16.3;18.7] | -9.25 [8.2;9.4]**† |
| GLPS A4C, % | -16.8 [15.9;19.2] | -9.9 [8.4;12.0] | -18.0 [14.5;18.8] | -9.8 [7.7;12.5]** |
| GLPS A2C, % | -18.7 [16.4;20.3] | -13.7 [11.8;15.1]** | -19.8 [17.6;22.1] | -12.6 [11.0;15.8]** |
| GLPS Avg, % | -18.7 [16.4;19.9] | -12.8 [11.5;14.3] | -18.3 [16.2;19.0] | -10.3 [9.2;12.0]**† |

Data are presented as Me [Q25; Q75]

**p<0.01 compared with the baseline value in the same group, †p<0.05 compared with the same parameter in the opposite group

CABG – coronary artery bypass grafting, GLPS LAX – the indicator of global LV deformation in the longitudinal direction from the five-chamber position, GLPS A4C – the indicator of global LV deformation obtained from the four-chamber position, GLPS A2C – the indicator of global LV deformation in the longitudinal direction from the two-chamber position, GLPS Avg – the average global LV deformation in the longitudinal direction

tions and shortening the duration of hospital stay including intensive care unit [10]. In particular, some researchers demonstrated that respiratory gymnastics contributed to lowering of the risk of postoperative bronchopulmonary complications [11], while physical training could optimize the prognosis and improve the life quality [12]. Generally, this strategy is considered to be effective and safe measure and contributes to organ protection.

Along with the available results, the search for new approaches is still continuing, in particular, the possibilities of pharmacological cardioprotection. In this aspect, drugs that have an effect on intracellular metabolism seem promising. Trimetazidine has a well-proven anti-ischemic action in the absence of hemodynamic effects, which makes it possible to use it in patients with ischemic etiology of heart failure [13]. According to the updated guidelines of the European Society of Cardiology (2019), trimetazidine is recommended as a second-line treatment for the symptoms controlling in patients with stable angina (class of evidence IIa, level B) [14]. Previous studies have shown that the administration of metabolic myocardial cytoprotectors (trimetazidine) before the surgery and in the early postoperative period of CABG definitely prevents myocardial damage associated with surgical intervention [15]. The results of the study by Yu.M. Lopatin et al. demonstrate the effectiveness of trimetazidine administration in the perioperative period regarding LV systolic function and exercise tolerance along with limiting of ischemia-reperfusion myocardial injury [16]. The obtained data are confirmed by the results of the work of V. Pichugin et al., which showed the efficacy of trimetazidine therapy via the implementation of the mechanism of pharmacological preconditioning of the myocardium [17]. The cardioprotective effect of trimetazidine, confirmed by the dynamics of markers of myocardial damage, finds also response in some foreign publications [18,19].

The results of this study have demonstrated that patients with different approaches to pharmacological therapy in the preoperative CABG period were characterised by similar course of the early postoperative period. The patients of the studied groups did not present clinical, laboratory and instrumental signs of myocardial damage using the routine clinical methods. At the same time, it was shown that patients who took trimetazidine as part of a comprehensive prehabilitation program demonstrated better perioperative dynamics of longitudinal LV deformation parameters compared to those who did not take trimetazidine. This may support the implementation of the cardioprotection mechanism.

According to the literature, a change in parameters of LV longitudinal deformation is registered in hypertensive patients more early comparing with the signs of LV hypertrophy and changes in the LVEF index [20]. At the same time, the parameters of deformation and strain rate represent markers of subclinical changes in the myocardium in CAD. Recent study by J.O. Choi et al. demonstrated that global and regional longitudinal deformation were significantly worse in patients with three-vessel coronary artery disease and preserved LVEF but without zones of impaired local contractility at rest [21]. It was shown that main parameters of LV longitudinal deformation correlated with the LVEF, which was confirmed by the results of this study, but at the same time these indicators represented more early predictors of the myocardial contractility impairment. In addition, the deterioration of longitudinal strain indicators was considered as a predictor of the heart failure progression [22].

Taking into account the literature data on the use of longitudinal strain indicators for early subclinical diagnostics of myocardial dysfunction, as well as the available knowledge about the cytoprotective mechanism of trimetazidine, it can be assumed that the results of this study indicate a possible implementation of the mechanism of cardioprotection in patients undergoing elective CABG. The limitation of the study is the lack of data on the indicators of LV longitudinal deformation during the long-term period after surgery. However, the results of functional six-minute walk test also support the proposed approach. In addition, it is recommended that the course of treatment with trimetazidine should be longer at the outpatient stage before performing CABG, that will contribute to more significant results, but further studies are required.

## Conclusion

The results of this study demonstrate the best postoperative dynamics of LV longitudinal deformation

indicators on administration of trimetazidine 80 mg/day as a component of prehabilitation of patients with CAD and planned CABG. In addition, significantly better indicators of exercise tolerance were also demonstrated according to the six-minute walk test results in this group of patients. This allows us to consider this approach to preoperative preparation effective from the perspective of possible cardioprotection and improvement of the functional status of patients after direct myocardial revascularization.

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