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The EXCEL Study: Long-term Observation of the Effectiveness of Drug and Non-drug Rehabilitation in Patients with Ischemic Heart Failure

Aim	To study the long-term effect of enhanced external counterpulsation (EECP) therapy on exercise tolerance, quality of life (QoL), and indicators of the structural and functional state of the cardiovascular system in patients with stable ischemic heart disease (IHD) complicated by chronic heart failure (CHF).
Material and methods	This open randomized EXCEL study included 120 patients with verified IHD complicated by NYHA II–III functional class CHF with reduced or mid-range left ventricular (LV) ejection fraction. Patients were randomized into group 1 (n=40), optimal drug therapy (ODT) and EECP (35 hours, 2 courses per year); group 2 (n=40), ODT and EECP (35 hours, 1 course per year); and group 3 (control; n=40), ODT and placebo counterpulsation (35 h, 1 course per year). All patients underwent a 6-minute walk test (6MWT), evaluation of clinical status, QoL with the MLHFQ and SF-36 questionnaires, structural and functional state of large blood vessels and microvasculature, measurement of brain natriuretic peptide precursor (NT-proBNP), and echocardiography at baseline and after 12 months.
Results	In groups 1 and 2 after 12 months, the 6MWT distance increased statistically significantly (44.5 and 24.9%, respectively) and the following indexes improved: QoL (SF-36, MLHFQ), the condition of large blood vessels (phase shift, radial augmentation index, central aortic systolic pressure (CASP)) and microvasculature (occlusion index, percentage of perfused capillaries, percentage of capillary recovery), and the LV systolic function (from 40.6±7.5 to 47.5±10.2% and from 41.3±6.8 to 43.9±10.3%, respectively). The proportion of patients with a >20% increase in the 6MWT at 12 months was 97.5, 72.5, and 7.7%, respectively. A statistically significant decrease in NT-proBNP was observed in all groups. In group 3, the incidence of hospitalizations for CHF and the risk of the composite endpoint were significantly higher.
Conclusion	For the 12-month study period, the effects of EECP in patients with IHD complicated by CHF included improvements in exercise tolerance, QoL, vascular and cardiac functional parameters, and a decrease in the incidence of adverse outcomes.

Keywords	Enhanced external counterpulsation; ischemic heart disease; chronic heart failure; exercise tolerance; vascular effects; quality of life
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Introduction

Cardiovascular diseases remain the most common causes of death and disability of the population worldwide with coronary artery disease (CAD) being the leader [1]. In the recent decades, there has been a notable decline in the mortality of patients with CAD and an increase in life expectancy due to improved medication management and an increased number of revascularization procedures performed. However, the limited duration of stent and graft functioning, and the lack of evidence of advantages in influencing the prognosis compared to the conservative management inevitably led to an increase in the percentage of patients with refractory angina pectoris [2]. Revascularization (stenting, grafting) is not possible in some patients due to comorbidities, anatomical features of coronary artery lesions or previous interventions. Moreover, these patients often have CAD complicated in by chronic

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heart failure (CHF), which further reduces quality of life (QoL) and functional reserve and complicates the full implementation of rehabilitation activities in patients of this category.

Limited possibilities of conservative and invasive management of patients with CAD complicated by CHF requires the search for new treatments that can effectively and safely supplement these two strategies. One of such methods is enhanced external counterpulsation (EECP), the effectiveness and safety of which were demonstrated by several studies [3–5]. Non-invasive nature, relatively low cost, and the possibility of use in outpatient settings are the advantages of this method. However, non-randomized designs, a small sample, or short duration of follow-up are the significant disadvantages of most of the studies, which requires conducting comprehensive randomized controlled studies.

Objective

Study the long-term effect of EECP therapy on exercise tolerance, QoL, the structural and functional state of the cardiovascular system in patients with stable CAD complicated by CHF.

Material and Methods

Prospective open-label randomized study EXCEL (Long-term Effects of enhanced eXternal CountErpuLsation) was conducted in the University Clinical Hospital No. 1 of I. M. Sechenov First Moscow State Medical University (Sechenov University) from 2017 to 2022. The study is registered at clinicaltrials.gov (NCT05913778).

The inclusion criteria were age from 40 to 75 years; verified stable CAD complicated by CHF class II–III (NYHA) with reduced (< 40%) or moderately reduced (40–49%) left ventricular ejection fraction (LVEF); the best possible drug therapy for stable CAD and CHF for at least 3 months before the inclusion; signed informed voluntary consent to participate in the study.

The exclusion criteria were acute coronary syndrome within < 6 weeks before the inclusion; coronary artery bypass grafting or percutaneous coronary intervention within < 6 months before the inclusion; history of thrombophlebitis and/or phlebitis; thoracic or abdominal aortic aneurysm; severe valvular heart pathology; severe pulmonary hypertension (grade 2–3); arrhythmias affecting the synchronization of an EECP device with electrocardiogram (ECG); decompensated CHF; uncontrolled hypertension (systolic blood pressure >180 mm Hg, diastolic blood pressure >110 mm Hg); coagulopathy; severe chronic lung diseases; cardiac catheterization within 4 weeks before the study; anticoagulant therapy with prothrombin time of > 15 s/international normalization ratio (INR) > 3; pregnancy, lactation; acute infectious/inflammatory diseases.

The withdrawal criteria included the onset of conditions listed among the exclusion criteria during the study or the patient's refusal to continue participating in the study.

A total of 212 patients with stable CAD complicated by CHF were examined. Of theme, 120 patients who met the inclusion/exclusion criteria were included in the study. CAD was verified based on a history of coronary angiography (CAG) without coronary artery stenting (n=9), CAG with coronary artery stenting (n=98) or coronary artery bypass grafting (n=25). 94 patients had a history of MI. CHF with reduced or mid-range LVEF was verified based on echocardiographic findings (LVEF < 40% or 40–49%, respectively) and elevated N-terminal pro-brain natriuretic peptide (NT-proBNP >125 pg/dL).

The local ethics committee of I. M. Sechenov First Moscow State Medical University approved the study protocol.

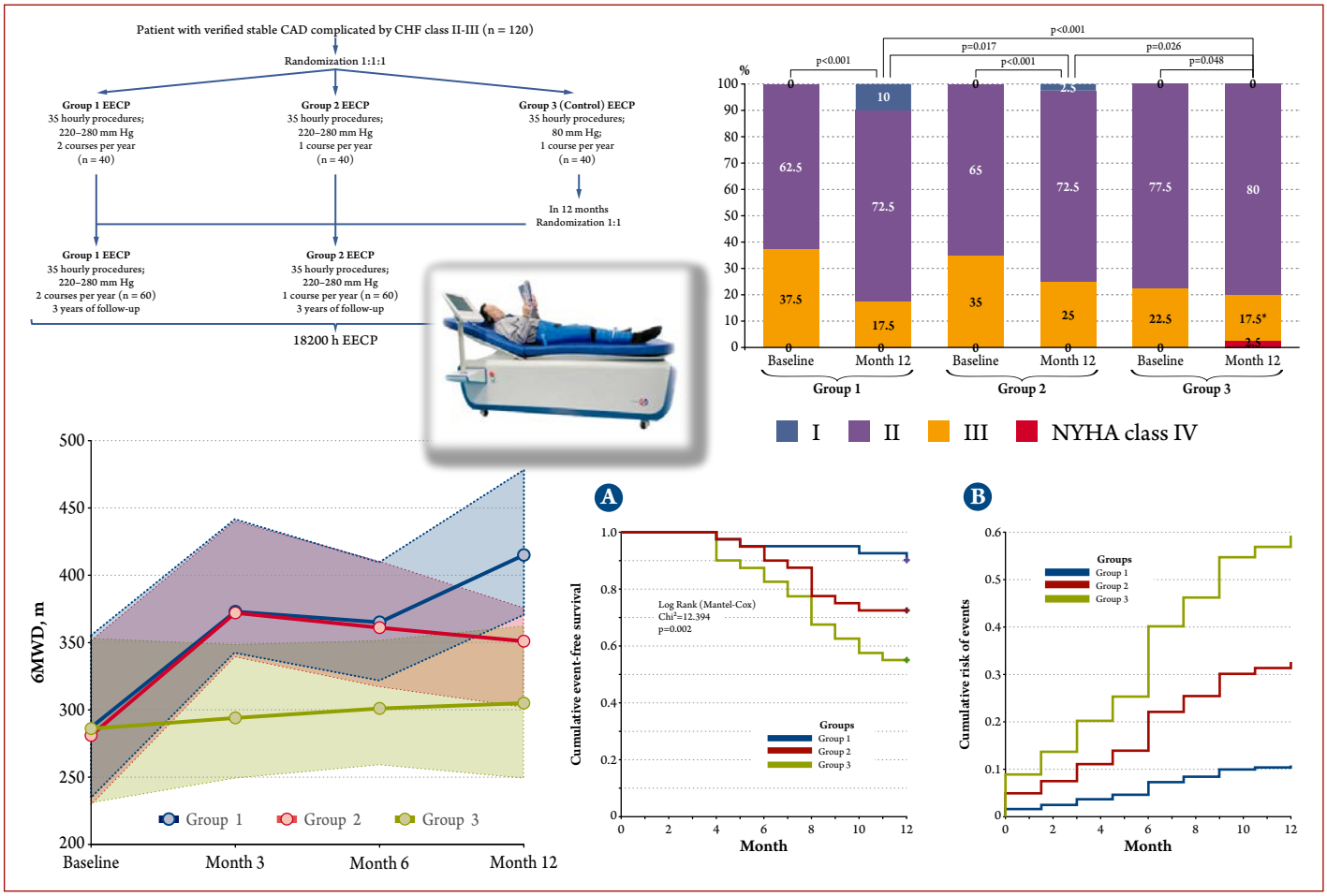
All patients included in the study were managed outpatiently, received the best possible drug therapy for CAD and CHF. All patients received renin-angiotensin-aldosterone system blocker (angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB)/valsartan/sacubitril), beta-blockers, mineralocorticoid receptor antagonists at adopted doses for at least 3 months before the inclusion.

The study design is presented in Figure 1.

Patients randomized using a random number generator (Statistica) in 3 groups with a 1:1:1 ratio. In Group 1, in addition to the best possible drug therapy, patients (n = 40) were subjected to EECP (35 hourly procedures, 5 procedures a week for 7 weeks; 2 courses a year every 6 months; compression pressure 220–280 mm Hg) using the EECP TS3 Therapy System. In Group 2, in addition to the best possible drug therapy, patients (n = 40) were subjected to EECP (35 hourly procedures, 5 procedures a week for 7 weeks; 1 course a year; compression pressure 220–280 mm Hg). In the control group, in addition to the best possible drug therapy, patients (n = 40) were subjected to placebo counterpulsation (35 hourly procedures, 5 procedures a week for 7 weeks; 1 course a year; compression pressure 80 mm Hg).

After 12 months, patients in the control group were randomized with a 1:1 ratio to Group 1 and Group 2.

Central Illustration



The safety of the EECP procedures was monitored by observing adverse reactions during the EECP procedures.

All patients underwent standard laboratory tests (complete blood count, urinalysis, biochemical blood tests: creatinine, fasting serum glucose, hepatic transaminases, creatine kinase, glycated hemoglobin in diabetes mellitus (DM)), NT-proBNP, standard examinations (ECG, echocardiography, 24-hour ECG monitoring, Doppler of the lower extremity vessels) at baseline, in 12, 24, and 36 months.

Addition examinations of were performed for all patients at baseline and in 3, 6, 12, 18, 24, and 36 months: clinical status (Symptomatic Hospital and Outpatient Clinical Score (SHOCS) by V. Yu. Mareev), exercise tolerance (6 minute walking distance (6MWD) test, QoL (SF-36 questionnaires, Minnesota Living with Heart Failure Questionnaire (MLHFQ)), vascular system condition (photoplethysmography (Angioscan-01), applanation tonometry (A-pulse CASPro), computerized nailfold video capillaroscopy (Capillaroscan-1).

This article presents the results of patient follow-up within the first 12 months of the study.

The primary endpoint was an increase in 6MWD distance by at least 20% at Month 12 compared to baseline. The secondary endpoints included changes in NYHA classes, QoL, occurrence of adverse cardiovascular clinical outcomes within 12 months of the study period, time to onset of new cases of atrial fibrillation (AF), DM, decreased renal function (a reduction in estimated glomerular filtration rate (eGFR) by at least 50% or by more than 30 mL/min/1.73 m^2 from the randomization level to less than 60 mL/min/1.73 m^2), and the development of the composite endpoint (CE): adverse outcomes, hospitalization for CHF, new cases of AF, DM, decreased renal function.

The statistical processing of data was carried out in Statistica 12.0 (StatSoft, USA).

The size of each group was 32 patients according to the calculation the study sample size (https://www.sealedenvelope.com/; alpha = 5%, 1 beta = 90%, non-inferiority limit = 10%), taking into account the effect size (changes in exercise tolerance in studies using EECP; 57% in the control group, 85% in the experimental group).

The data are presented as the medians and the interquartile ranges (Me [25th percentile; 75th

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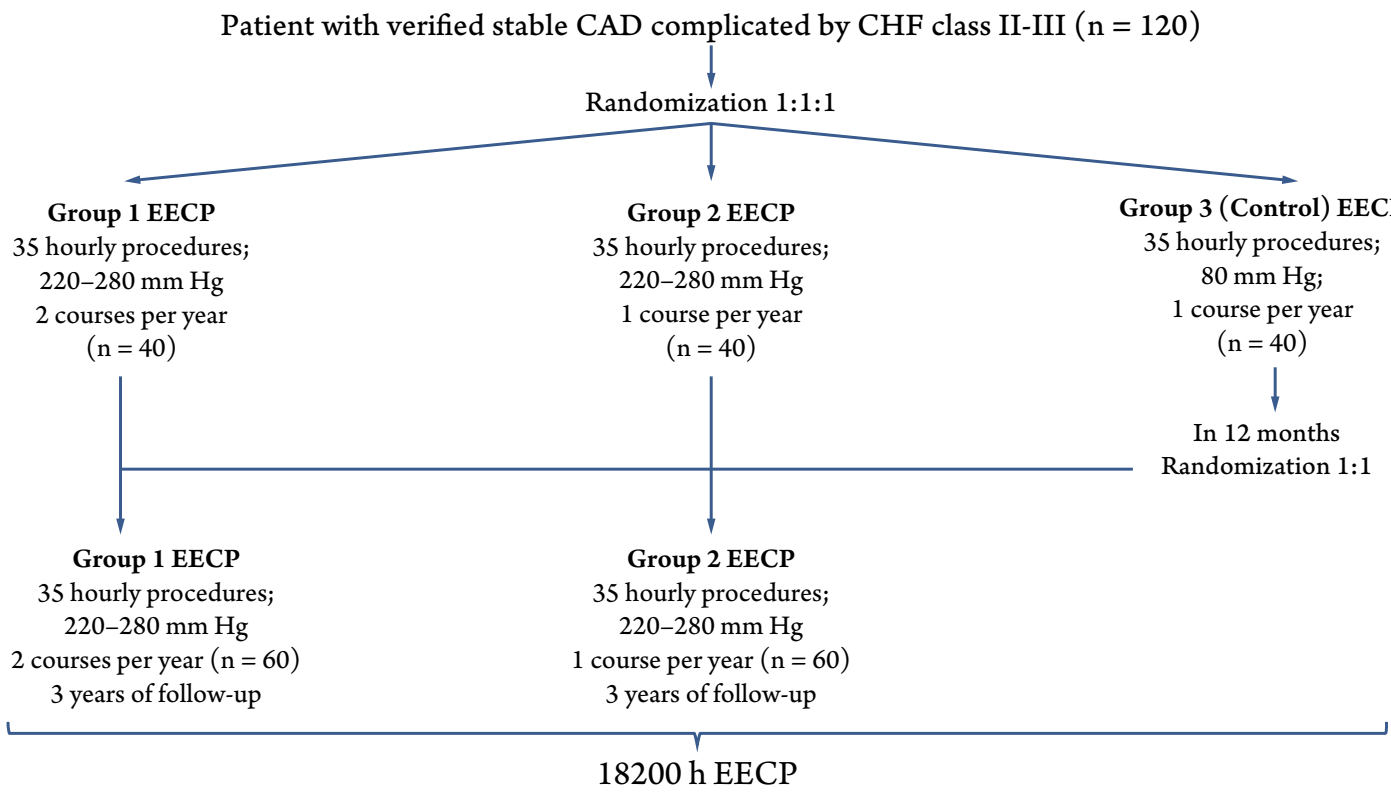
Figure 1. Study design



CAD, coronary artery disease; CHF, chronic heart failure; ECP, external counterpulsation; EECP, enhanced external counterpulsation.

percentile]). To compare the groups, the Mann-Whitney U test was used for quantitative and qualitative ordinal variables and the two-tailed Fisher exact test was used for categorical variables. The Wilcoxon test and the McNemar chi-square test were used for quantitative and qualitative ordinal variables and categorical variables, respectively, to evaluate changes from baseline (within each group). When evaluating the changes in quantitative and qualitative ordinal variables compared to the baseline, delta was also calculated using the formula:

$$\Delta\,\% = N1 - N0/N0 \times 100\%,$$

where N0 is a baseline value, N1 is a value changed over time. The Kaplan-Meier analysis evaluated the survival function in the study groups. The differences were statistically significant at a two-tailed level of significance of $p<0.05$.

Results

Characteristics of the study groups

The groups were comparable in the main clinical and demographic characteristics (Table 1).

The patients tolerated EECP satisfactorily during the study period. The side effects were erections during EECP procedures in 4 (10%) male patients Group 1 and 3 (7.5%) male patients in Group 2.

Quality of life and exercise tolerance

During the study period (12 months), positive changes in CHF class was observed in all groups, although mean CHF class changed only in Group 1 (from 2.38 to 2.08) and Group 2 (from 2.35 to 2.23), but not in Group 3 (from 2.23 to 2.23; Figure 2).

As for changes in exercise tolerance in patients undergoing EECP, an increase in 6MWD was noted in all groups, but the changes were statistically significant only in Group 1 (by 44.5%) and Group 2 (by 24.9%), but not in Group 3 (by 6.6%; Figure 3). At the same time, the percentage of patients with a longer 6MWD by > 20% was 97.5%, 72.5%, and 7.7%, respectively, in 12 months.

The estimation of changes of QoL in the EECP group showed a statistically significant improvement in the MLHFQ score and the physical and mental health scores according to the SF-36 questionnaire (Table 2).

Structural and functional condition of the cardiovascular system

According to photoplethysmography and applanation tonometry, a statistically significant positive 12-month changes in functional indicators of the major vessel condition (phase shift, central aortic systolic pressure) and radial augmentation index reflecting the characteristics of aortic stiffness were

Table 1. Clinical and demographic characteristics of the study groups

Parameter	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	p
Age, years	64.0 [57.5; 70.3]	63.5 [56.8; 70.0]	64.1 [57.5; 69.8]	0.534
Male, n (%)	32 (80.0)	31 (77.8)	34 (83.6)	0.347
CAD course, years	6.6 [5.2; 10.7]	7.0 [6.0; 11.0]	7.1 [5.5; 11.2]	0.274
CHF course, years	4.0 [2.6; 7.3]	4.1 [2.2; 6.9]	3.9 [2.5; 7.5]	0.450
HFrEF, n (%)	21 (52.5)	19 (47.5)	22 (55.0)	0.304
HFmrEF, n (%)	19 (47.5)	21 (52.5)	18 (45.0)	0.280
BMI, kg/m2	29.0 [27.1; 35.0]	28.7 [26.9; 35.2]	28.5 [26.2; 35.0]	0.678
GFR (CKD EPI), mL/min/1,73 m^2	68.2 [53.1; 80.0]	66.7 [54.0; 81.5]	67.2 [54.1; 78.0]	0.506
SBP/DBP, mm Hg	124 [117; 136] / 77 [73; 86]	126 [118; 136] / 78 [73; 85]	126 [114; 137] / 77 [72; 86]	0.612
HR, bpm	66 [56; 74]	65 [55; 73]	66 [58; 74]	0.606
Glucose, mmol/L	5.9 [5.6; 7.6]	5.5 [5.4; 7.2]	5.7 [5.6; 7.4]	0.208
HbA1c, %	5.9 [5.4; 6.4]	5.8 [5.3; 6.5]	5.9 [5.3; 6.6]	0.267
TC, mmol/L	5.6 [5.0; 6.4]	5.7 [5.1; 6.6]	5.6 [5.1; 6.3]	0.378
LDL cholesterol, mmol/L	2.0 [1.3; 2.5]	1.9 [1.3; 2.4]	1.9 [1.3; 2.6]	0.409
NT-proBNP, pg/mL	240 [160; 320]	232 [156; 330]	236 [158; 332]	0.201
Smoking, n (%)	6 (15.0)	6 (15.0)	8 (20.0)	0.190
Multivessel coronary artery disease, n (%)	7 (17.5)	8 (20.0)	9 (22.5)	0.227
History of MI, n (%)	30 (75.0)	31 (77.5)	33 (82.5)	0.211
Coronary artery stenting, n (%)	32 (80.0)	32 (80.0)	33 (82.5)	0.690
CABG, n (%)	9 (22.5)	7 (17.5)	9 (22.5)	0.300
Hypertension, n (%)	27 (67.5)	29 (72.5)	27 (67.5)	0.443
DM type 2, n (%)	20 (50.0)	21 (52.5)	20 (50.0)	0.509
AF, n (%)	5 (12.5)	4 (10.0)	4 (10.0)	0.398
CKD stage 3-5, n (%)	14 (35.0)	12 (30.0)	15 (37.5)	0.267
RAAS blockers, n (%)	40 (100.0)	40 (100.0)	40 (100.0)	1.000
Beta blockers, n (%)	40 (100.0)	40 (100.0)	40 (100.0)	1.000
MRAs, n (%)	40 (100.0)	40 (100.0)	40 (100.0)	1.000
Nitrates, n (%)	21 (52.5)	21 (52.5)	20 (50.0)	0.546
Diuretics, n (%)	35 (87.5)	34 (85.0)	35 (87.5)	0.567
Hypoglycemic therapy, n (%)	20 (50.0)	21 (52.5)	20 (50.0)	0.589
Statins, n (%)	40 (100.0)	40 (100.0)	40 (100.0)	1.000

The data is presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]) if not otherwise specified. CAD, coronary artery disease; CHF, chronic heart failure; FC, functional class; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; BMI, body mass index; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HbA1c, glycated hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; MI, myocardial infarction; CABG, coronary artery bypass grafting; DM, diabetes mellitus; AF, atrial fibrillation; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; MRA, mineralocorticoid receptor antagonist.

observed in Group 1 (Table 3). Moreover, in Group 1, there was a statistically significant improvement in occlusion index reflecting the functional condition of the microcirculatory system Changes in structural indicators of the major vessels (stiffness index) and microcirculatory system (reflection index) were statistically insignificant. In 12 months, there was also a statistically significant increase in LV contractile function in Group 1 (more pronounced) and Group 2. A statistically significant decrease in NT-proBNP was shown in all groups, with a statistically significantly greater decrease in Group 1 compared to Group 2 and Group 3.

Primary and secondary endpoints

The percentages of patients with a longer 6MWD by > 20% after 12 months (primary endpoint) was 97.5%, 72.5%, and 7.7% in Group 1, Group 2, and Group 3, respectively.

Frequency of secondary endpoints in study groups is provided in Table 4.

The cases of hospitalization for CHF and the development of CE were statistically significantly more frequent in Group 3 (Table 4). The log-rank analysis showed that the cumulative survival was significantly higher in Group 1 and Group 2 than in Group 3, and the cumulative risk of events in the latter group was thus maximum (Figure 4).

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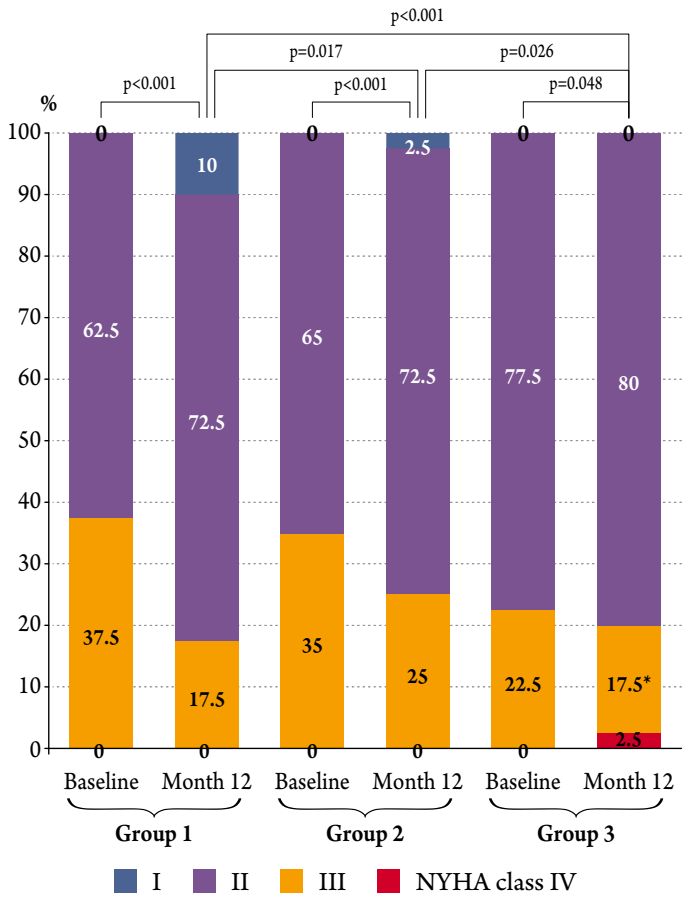
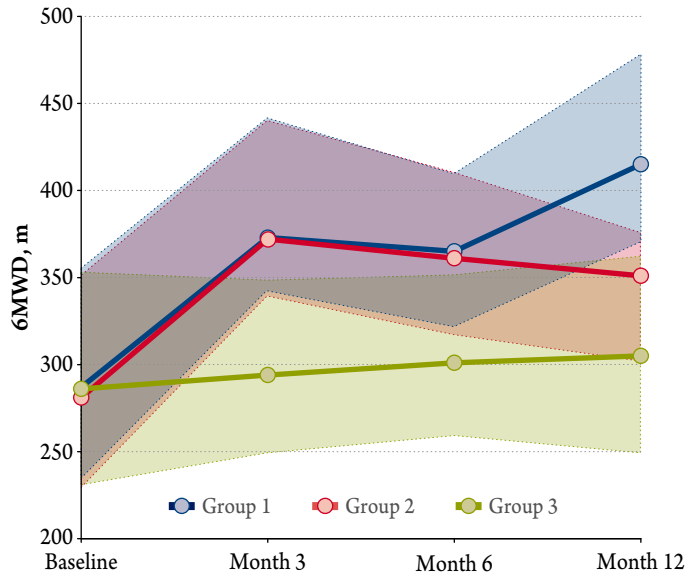
Figure 2. Cahanges in CHF classes during the follow-up



FC, functional class.
* – the latest available data are presented for one deceased patient.

Figure 3. Changes in the 6-minute walking distance



Группы	Baseline	Month 3	Month 6	Month 12	p
Group 1	287 [235; 354]	373 [242; 441]	365 [321; 409]	415 [371; 478]	0.007
Group 2	281 [230; 351]	372 [339; 440]	361 [317; 410]	351 [302; 375]	0.014
Group 3	286 [231; 352]	294 [249; 348]	301 [259; 351]	305 [250; 362]	0.058
p	0.239	0.012	0.034	0.009	–

6MWD, 6 minute walking distance.
The data are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]).

Table 2. Changes in the parameters of quality of life

Parameter	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 39)	p
SF-36, score				
Baseline	44.5 [40.5; 51.2]	45.1 [41.2; 53.4]	46.1 [41.5; 54.0]	0.234
Month 12	50.5 [46.1; 53.1]	49.1 [44.5; 55.0]	47.4 [43.0; 53.1]	0.064
Changes, Δ	6.0 [0.4; 10.6]	3.8 [0.2; 6.1]	1.7 [0.2; 5.2]	0.043
$P_{base-month\ 12}$	0.004	0.048	0.079	–
SF-36 MH, score				
Baseline	48.0 [45.8; 54.7]	49.1 [45.4; 55.4]	48.5 [44.4; 55.6]	0.671
Month 12	54.4 [49.9; 60.8]	52.3 [43.5; 53.1]	52.0 [42.4; 53.4]	0.610
Changes, Δ	4.5 [2.1; 7.1]	2.4 [1.0; 5.4]	1.7 [-0.3; 5.0]	0.038
$P_{base-month\ 12}$	0.005	0.051	0.067	–
MLHFQ, score				
Baseline	63.1 ± 16.2	62.5 ± 15.7	62.0 ± 15.8	0.208
Month 12	31.6 ± 7.8	47.5 ± 13.8	53.0 ± 14.0	0.012
Changes, Δ	28.0 ± 5.7	14.8 ± 5.5	8.6 ± 6.3	< 0.001
$P_{base-month\ 12}$	0.002	0.048	0.061	–

PH, physical health; MN, mental health, MLHFQ – Minnesota Living with Heart Failure Questionnaire. The data are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]) or the absolute numbers and percentages (n (%)).

Table 3. Changes in the cardiovascular parameters

Parameter		Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 39)	p
SI, m/s	Baseline	8.0 ± 1.6	8.3 ± 1.5	8.2 ± 1.5	0.383
	Month 12	8.6 ± 1.5	8.5 ± 1.4	8.4 ± 1.5	0.302
	$P_{base–M12}$	0.069	0.332	0.298	–
RI, %	Baseline	38.9 ± 10.9	36.9 ± 11.4	38.0 ± 10.5	0.341
	Month 12	36.5 ± 13.1	34.4 ± 12.5	37.1 ± 11.0	0.054
	$P_{base–M12}$	0.053	0.068	0.101	–
PS, m/s	Baseline	5.6 ± 1.4	5.8 ± 1.5	5.6 ± 1.5	0.595
	Month 12	7.2 ± 1.3	6.1 ± 1.6	5.8 ± 1.5	0.806
	$P_{base–M12}$	0.015	0.067	0.112	–
IO	Baseline	1.50 ± 0.30	1.51 ± 0.34	1.51 ± 0.33	0.540
	Month 12	1.65 ± 0.30	1.52 ± 0.32	1.52 ± 0.34	0.043
	$P_{base–M12}$	0.002	0.333	0.346	–
rAI, %	Baseline	97.3 ± 25.2	96.6 ± 24.7	97.2 ± 23.4	0.870
	Month 12	90.3 ± 21.6	94.7 ± 24.0	95.3 ± 22.8	0.148
	$P_{base–M12}$	0.012	0.067	0.078	–
CASP, mm Hg	Baseline	129.0 ± 13.5	127.5 ± 11.1	128.2 ± 13.0	0.595
	Month 12	123.4 ± 12.8	126.0 ± 11.0	127.0 ± 12.0	0.023
	$P_{base–M12}$	0.010	0.056	0.061	–
CD rest, cap/FOV	Baseline	44.0 ± 12.2	45.1 ± 11.9	45.0 ± 12.0	0.458
	Month 12	45.1 ± 10.8	45.3 ± 11.0	45.2 ± 10.7	0.544
	$P_{base–M12}$	0.097	0.109	0.121	–-
PC, %	Baseline	88.9 ± 5.8	87.5 ± 6.2	87.3 ± 6.0	0.666
	Month 12	92.3 ± 6.3	90.0 ± 5.9	88.0 ± 6.1	0.041
	$P_{base–M12}$	0.012	0.023	0.065	–
CR, %	Baseline	8.0 ± 3.5	8.7 ± 3.6	8.3 ± 3.6	0.618
	Month 12	15.6 ± 6.8	11.1 ± 4.5	8.4 ± 4.1	0.035
	$P_{base–M12}$	< 0.001	0.013	0.211	–
LVEF, %	Baseline	40.6 ± 7.5	41.3 ± 6.8	42.0 ± 7.0	0.560
	Month 12	47.5 ± 10.2	43.9 ± 10.3	43.2 ± 8.9	0.022
	$P_{base–M12}$	0.012	0.041	0.069	–
NT-proBNP, pg/mL	Baseline	240 [160; 320]	232 [156; 330]	236 [158; 332]	0.201
	Month 12	121 [96; 155]	154 [110; 196]	169 [122; 201]	0.023
	$P_{base–M12}$	< 0.001	0.012	0.027	–

SI, stiffness index; RI, reflexion index; PS, phase shift; OI, occlusion index; rAI – radial augmentation index; CASP, central aortic systolic pressure; CD, capillary density; PC, perfused capillaries; CR, capillary recovery; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide. The data are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]) or the absolute numbers and percentages (n (%)).

Discussion

The EXCEL study is one of the first randomized studies of using EECP in Russia. Of 212 patients, 120 patients who met the inclusion/exclusion criteria were selected and included in the study and the final analysis. All patients underwent a total of 5600 h of external counterpulsation procedures within the first 12 months of the study (including placebo procedures in Group 3).

EECP tolerance was satisfactory. The reported side effects were erections during EECP procedures in 4 (10%) male patients Group 1 and 3 (7.5%) male patients in Group 2. It should be noted that the patients were irritated by this side effect during the procedures only from the aesthetic point of view. According to Wu et al. [6], soreness at the cuff site, skin damage, leg paresthesia were the most common side effects during the EECP procedures. In our experience, careful selection of patients for EECP given contraindications, the correct application of cuffs and the selection of compression mode can significantly reduce the number or prevent side effects.

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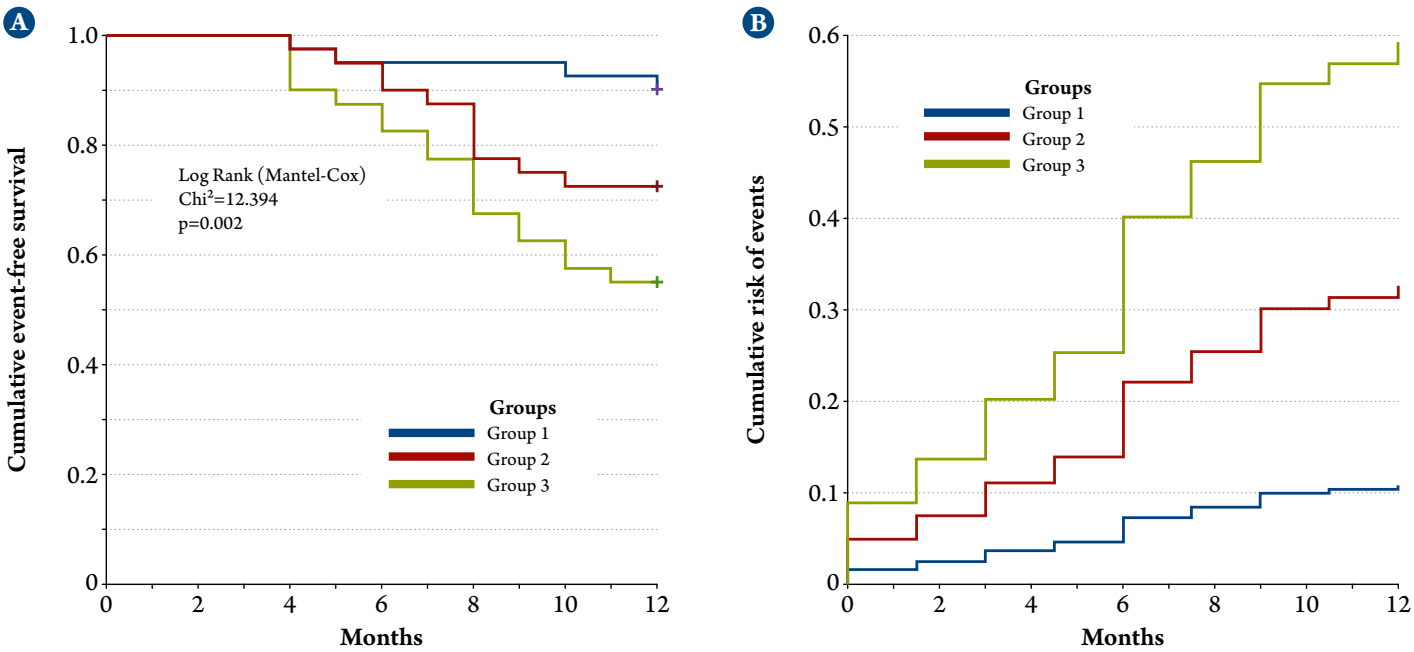
Table 4. Frequency of secondary endpoints in study groups

Parameter	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	p
MI, n (%)	1 (2.5)	2 (5.0)	2 (5.5)	0.811
PCI/CABG, n (%)	1 (2.5)	3 (7.5)	3 (7.5)	0.545
Death, n (%)	0	0	1 (2.5)	–
Hospitalization for CHF, n (%)	1 (2.5)	2 (5.0)	7 (17.5)	0.033
New cases of AF, n (%)	0	2 (5.0)	2 (5.0)	–
New cases of DM, n (%)	0	1 (2.5)	2 (2.5)	–
New cases of decreased renal function, n (%)	1 (2.5)	1 (2.5)	1 (2.5)	1.000
CE, n (%)	4 (10.0)	11 (27.5)	18 (45)	0.002

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, chronic heart failure; AF, atrial fibrillation; DM, diabetes mellitus; CE, composite endpoint.

Figure 4. Analysis of survival (A) and cumulative risk (B) in the study groups



The relationship between erectile dysfunction and CAD and the ability of EECP to improve erectile function in male patients has already been reported [7, 8]. Jackson et al. [9] indicate that CAD develops a mean of 2–3 years after the onset of erectile dysfunction, and the initiation of EECP improved the course of both CAD and erectile dysfunction.

The positive effect of EECP on the clinical status and QoL of patients was confirmed in several previous studies [3, 4, 10, 11]. In our study, the SF-36 and MLHFQ questionnaires were used to evaluate the effect of EECP on QoL. A statistically significant positive effect on both the physical and mental health was observed in the EECP groups in all study periods and was more pronounced in Group 1 with 2 courses per year. Visiting the procedures for 7 weeks is likely to organize the patient's behavior, increase treatment adherence, and physical and social activity. It should be noted that a statistically significant positive changes in some SF-36 indicators was also observed in the placebo group in the period of 3–6 months. This moment will be studied in future.

The assessment of exercise tolerance showed that 6MWD increased statistically significantly in 12 months only in groups with 2 (44.5%) or 1 (24.5%) course of EECP a year. The percentages of patients with a longer 6MWD by > 20% after 12 months (primary endpoint) were 97.5%, 72.5%, and 7.7%, respectively.

According to the meta-analysis by Zhou et al. [12], EECP treatment caused a statistically significant increase in 6MWD (+84.79 m; 95% confidence interval (CI) 47.64–121.95; p < 0.001) and LVEF (standardized mean differences 0.64; 95% CI 0.29–1.00; p = 0.0004), and a decrease in NT-proBNP (standardized mean differences –0.61; 95% CI –1.20 – –0.01; p=0.04). However, EECP did reduced statistically significantly the MLHFQ scores

compared to the control (weighted mean differences –9.28; 95% CI –19.30–0.75; p = 0.07) [12].

The study of the effects of LVEF on 12-month changes of structural and functional indicators of the cardiovascular system showed positive changes in the predominantly functional state of both the heart (LVEF) and major vessels (PS, Casp, rAI) and the microcirculatory system (RI, AUC, PCV). Previous studies also showed the positive effect of EECP on the condition of major vessels and the microcirculatory system (beta-stiffness index and resistance index) of the carotid system [13], and the endothelial function (improved flow-dependent vasodilation) [14]. It should be noted that the vascular effects of EECP do not last for more than 3–6 months after the course of EECP as was shown by us earlier [15]. Therefore, patients with CAD, including complicated by CHF, should receive EECP either 2 courses per year or in another intermittent regimen (every other day, 2 times a week, etc.) for a longer time.

The LV contractile function improved and NT-proBNP levels decreased in all groups during the 12 month period, however, a statistically significant increase in the LVEF was only observed in the EECP groups. The positive changes in these indicators in the placebo counterpulsation group can be explained by the adequate drug therapy and good treatment adherence. Improved myocardial contractile function during EECP treatment was also demonstrated in numerous studies and the meta-analysis [4, 11]. Xu et al. [11] showed that the standard EECP course not only improves systolic myocardial function but also reduces the frequency of repeated hospitalizations and seeking emergency care within 6 months after the course. In our study, the frequency of hospitalizations for CHF decreased statistically significantly in the EECP groups in the 12 month study period.

According to Sahlén et al. [16], EECP treatment leads to an increase in exercise tolerance and a decrease in NT-proBNP level, and the size of the effect was the greater the more pronounced functional disorders and the higher levels of NT-proBNP.

The study of changes in the secondary endpoints showed a statistically significant decrease in the incidence of CE (a combination of cases of adverse outcomes, hospitalization for CHF, the development of new cases of AF, DM, and decreased kidney function), and the risk of their development in the group of patients with 2 courses of EECP a year (p = 0.002).

According to the Expert Consensus on the Clinical Use of EECP in Older Persons [17], there has been a shift from studying only hemodynamic effects of EECP to assessing vascular and tissue effects. At the same time, the unique hemodynamic effects of EECP (an increase in diastolic aortic pressure by 26–157%, cardiac output by a mean of 25%, intracoronary diastolic pressure by 16%, and coronary blood flow rate by a mean of 109%) makes it possible to successfully use this method in CAD and CHF in polymorbid elderly patients [17].

In most studies of EECP in patients with CAD, including complicated by CHF, the effects were evaluated 0–12 months after the completion of the standard single course (35 hours a year) [10, 18–20]. Our experience shows that the effects of EECP do not usually persist in these patients for more than 6 months. Therefore, one of our tasks was to demonstrate the time-limited effects of EECP. The variability of non-vascular effects (exercise tolerance, QoL) was significantly higher compared to the vascular effects both in terms of their size and duration. This may be due to the variety of functional phenotypes of patients (ratio of the coronary system functional reserve and the muscular system). The follow-up results of this study will be presented in the following publications.

Limitations

Despite the sufficient power of the study, it would be desirable for such studies to have larger samples from several sites, but this is not always possible due to technical and organizational difficulties. Even in large multicenter MUST-EECP study, only 139 patients were recruited at 7 sites [4].

The relatively long duration of the study (about 7 years) makes it difficult to assess the best possible drug therapy for CHF due to changes introduced over time and the adoption of new clinical guidelines.

The evaluation of vascular effects and exercise tolerance was carried out using the available methods (photoplethysmography, capillaroscopy, applanation tonometry, 6MWD test) rather that gold standards (flow-dependent vasodilation, cardiopulmonary stress test), which must also be taken into consideration during the interpretation of the results.

Conclusion

The randomized EXCEL study demonstrated a positive effect of enhanced external counterpulsation in patients with coronary artery disease complicated by chronic heart failure on exercise tolerance, quality of life, functional parameters of the vascular system and heart, which depended on the exposure time of enhanced external counterpulsation procedures. The inclusion of enhanced external counterpulsation in the comprehensive cardiac rehabilitation program for

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this category of patients can contribute to increasing its efficacy, even in patients with low functional reserve, and the adherence of patients to treatment and rehabilitation activities. The possibilities of enhanced external counterpulsation are still being studied, however, many mechanisms and effects of this therapy remain unknown, which requires further research.

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