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Tolerability of an Individualized Physical Rehabilitation Program in Patients Dependent on Inotropic Support With End-Stage Chronic Heart Failure

Aim	To assess the tolerability of an individualized physical rehabilitation program (PRP) in inotrope-dependent patients with end-stage chronic heart failure (CHF).
Material and methods	This prospective randomized study included 120 men aged 18-65 years with left ventricular ejection fraction ≤30% and blood pressure ≥90/60 mm Hg. Patients who have received dobutamine or dopamine for ≥2 weeks were randomized into two groups: group 1, 40 patients who participated in the PRP and group 2, 40 patients who did not participate in the PRP. Group 3 included 40 patients without inotropic support who participated in the PRP.
Results	Patients of groups 1 and 3 attended >80% of the scheduled classes without developing life-threatening adverse events (AEs) associated with exercise (E). After 6 months of the study, the exercising patients achieved a comparable (average) E intensity: 44 [35; 50]% and 45 [40;52]% of heart rate reserve and Borg scale scores 14 [12; 14] and 13 [11; 14] in groups 1 and 3, respectively (p>0.05). Initially, after 3 and 6 months at the peak of physical activity in groups 1 and 3, there was no decrease in arterial blood oxygen saturation according to pulse oximetry (SpO2) <93%. At baseline, lactate levels in central venous blood at rest were normal in all groups. After 6 months, the lactate concentration was 1.1 mmol/l in group 1, 2.3 mmol/l in group 2, and 1.4 mmol/l in group 3 (p1-2=0.005; p2-3=0.008, respectively). At the E peak at baseline, after 3 and 6 months, comparable increases in lactate not exceeding 3 mmol/l were detected in groups 1 and 3.
Conclusion	The study allowed assessment of the tolerability of individualized PRP performed at the aerobic level of energy supply, in inotropic-dependent patients with CHF. Individualized 6-month PRP in inotropic-dependent patients with end-stage CHF, provided safety criteria are met, is well tolerated and does not increase the number of AEs associated with CHF and physical rehabilitation (PR). Continued inotropic support with dopamine or dobutamine should not be considered as a contraindication to PR in patients with CHF in the absence of E intolerance or life-threatening AEs.

Keywords	Terminal chronic heart failure; dopamine; dobutamine; physical rehabilitation; exercise
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Introduction

Patients with inotropic dependence (inotrope-dependent patients) with end-stage CHF are the most unfavorable group in terms of prognosis; their 6-month mortality reaches 78% [1]. Hypodynamia inevitably accompanying severe chronic heart failure (CHF) contributes to the deterioration of exercise tolerance, the progression of myopathy, cachexia, and sarcopenia [2–4], and also increases the risk of thromboembolism (TE) [5] and pneumonia [6, 7]. The search for optimal physical rehabilitation (PR) of patients with stable CHF [8] and the evaluation of predictors of success [9] is ongoing. However, PR of inotrope-dependent patients is given little attention in medical literature and is not included into CHF treatment guidelines due to the lack of its safety and efficacy evidence.

Objective

To evaluate tolerability of an personalized physical rehabilitation program (PRP) by inotrope-dependent patients with end-stage CHF.

Material and Methods

The prospective randomized study included 120 patients hospitalized in the Almazov National Medical Research

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Center (Russian Federation). The study protocol was approved by the ethics committee of the facility. End-stage CHF was diagnosed according to the criteria of the European Society of Cardiology [10].

Inclusion criteria: signed informed consent to participate in the study; male aged 18–65 years old with end-stage CHF class III–IV; dilated cardiomyopathy; coronary artery disease, LVEF≤30% (Simpson's method); BP ≥90/60 mm Hg (sitting); optimal therapy for CHF; administration of dopamine or dobutamine (if indicated) for ≥ 2 weeks.

Exclusion criteria: unstable hemodynamics; progression of CHF; sustained paroxysms of ventricular tachycardia (VT) during the discussed hospital treatment; resting HR>100 bpm; unstable angina<1 month, myocardial infarction and TE<3 months, acute cerebrovascular accident<6 months; concomitant pathology worsening the 6 month prognosis.

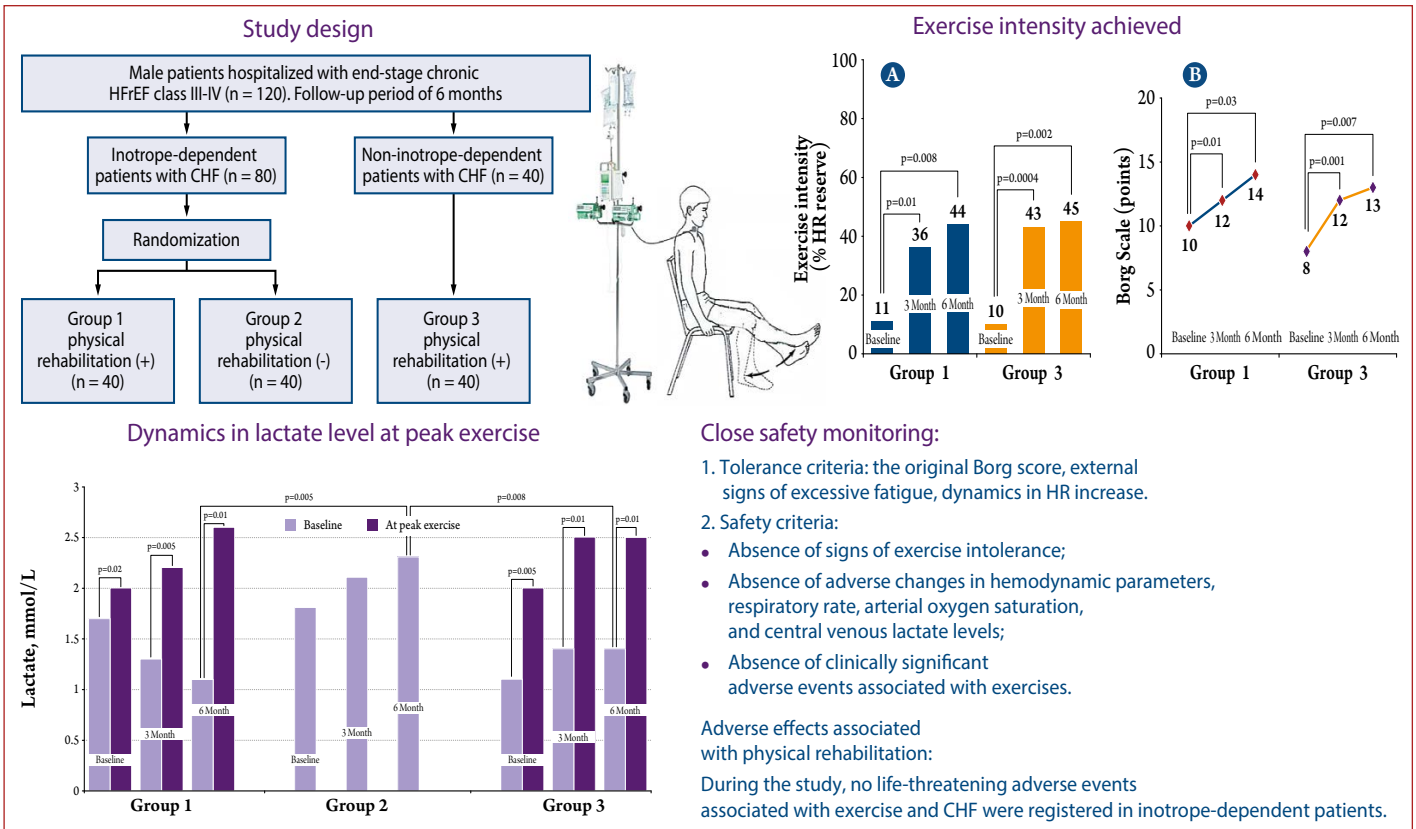
Study design

Patients treated with dobutamine or dopamine were randomized by envelope method into 2 groups of 40 male each: Group 1 – patients who participated in the PRP, Group 2 – patients who did not participate in the PRP. Group 3 included 40 inotrope-independent patients who participated in the PRP. The follow-up period was 6 months. Initially, after 3 and 6 months, echocardiographic parameters at rest and lactate level in central venous blood were evaluated in all groups; lactate level at peak of exercise was evaluated in Group 1 and Group 3. Exercise tolerance criteria, adverse events (AEs), SpO2 (%), BP, respiratory rate (RR) were estimated in Group 1 and Group 3 at each exercise therapy session (before the session, in the main and final parts, 10 minutes and 1 hour after its completion).

Components of physical rehabilitation program

1. Educational module - informing patients about physical activity in CHF, education of self-control and safe exercise performaning.
2. Therapeutic positioning – change of position in bed every 2 hours – for patients with physical activity modes 1b and 2.

Central illustration. Tolerability of an Individualized Physical Rehabilitation Program in Patients Dependent on Inotropic Support With End-Stage Chronic Heart Failure



3. Therapeutic exercises (TE) – 4 therapeutic exercise complexes (TEC) were developed: № 1 – very low intensity, № 2 – low intensity, № 3 – low-moderate and № 4 – moderate intensity. Controlled therapeutic exercise sessions were conducted 5 times a week. The exercise intensity and its total dose per day were regulated by the starting position, the character of exercises, the number of repetitions, the duration of a session and the number of sessions per day. In Group 1 and Group 3 the sessions began with complex № 1. The time of transition to the next complex was determined individually. The criterion of transition to the next complex was a stable (for 7 consecutive sessions) mastering of the current complex, namely: performance of the maximum target number of exercises within the time interval defined for each TEC. In all complexes, dynamic exercises for small and medium muscle groups were used in the introductory and final part of a session; in the main part included dynamic exercises for medium muscle groups of upper and lower limbs; dynamic exercises for medium muscle groups of upper and lower limbs with a strength (resistive) component, dynamic and static breathing exercises. TEC № 1–4 differed in the duration of a session 1 (from 6 to 20 minutes), number of sessions per day – from 4 (TEC № 1) to 2 (TEC № 3–4), total daily duration of exercise sessions – from 20 minutes (TEC № 1) to 40 minutes (TEC № 4), starting position (TEC № 1 – lying, TEC № 2-sitting, TEC № 3–4 – sitting, standing), the number of exercises and the time of the main (loading) part of the complex, the ratio of general strengthening exercises to special exercises within in the complexes (TEC № 1–2 – 2:1, TEC № 3–4 – 1:1); breathing exercises (dynamic breathing and static breathing, diaphragmatic breathing) and resistive exercises were used as special in all complexes. The number of breathing and resistive exercises was minimal in TEC № 1 (2 and 1, respectively); in TG complexes № 3 and 4 it was 6–8 and 4–7 respectively. Exercise intensity was controlled using the Borg scale, an increase in HR, and external signs of excessive fatigue.
4. Controlled walking in addition to TEC № 3–4. Exercise intensity was controlled by walking speed (calculated individually based on 6 minute walking distance test results and modified according to the changes of exercise intensity), duration of controlled walking (1 → 15 min; the duration increased by 1 min/day) and frequency (1 → 2 times a day). Controlled walking intensity was regulated in the same way as for therapeutic exercises.

The safety of performing TEC № 1–3 in the wards of the cardiology department was monitored using bedside monitors, and TEC № 4 – in the wards and halls of the department – was monitored using portable monitors by the attending physician and the physiatrist or exercise therapist. The session was discontinued if the safety criteria were not met, or patients refused to continue it.

PRP tolerance criteria:

1) *Subjective:* a patient's self-assessment of the effort required to perform an exercise using the original (15 point) Borg scale [11]; the need to discontinue the exercise earlier, a decrease in exercise rhythm and/or intensity;
2) *Objective:* development of external signs of excessive fatigue [12]; changes in HR: an increase in HR versus rest≤15% of HR reserve during exercise of very low-intensity,≤25% – of low intensity,≤40% – of low-moderate intensity,≤55% – of moderate intensity. The HR reserve was determined by the formula [220 – age – resting HR] [13].

PRP safety criteria:

1) Exercise tolerance: no signs of poor tolerance;
2) Hemodynamic parameters and RR: resting sitting BP ≥ 90/60 mm Hg, during exercise – no decrease in systolic BP (SBP) versus baseline >10 mm Hg, or SBP<80 mm Hg, or an increase in SBP>160 mm Hg; resting HR ≤100 bpm, during exercise – no decrease in HR versus baseline or increase>130 bpm, or>60% of the HR reserve; RR during exercise≤35 brpm;
3) Absence of exercise-associated AEs: syncope, induction of paroxysms of atrial fibrillation, atrial flutter, VT, and activation of implantable cardioverter-defibrillator (ICD), ACS, PE, progression of CHF, ischemic changes in the electrocardiogram, death. Cardiac rhythm disturbances and ischemic changes were evaluated using Beneview T5 monitors;
4) Echocardiography parameters;
5) Six month prognosis: no increase in the number of episodes of acute decompensated CHF and cardiovascular death compared to the control group;
6) Arterial oxygen saturation (SpO2) by pulse oximetry>95% at rest and >90% at peak exercise, lactate ≤2.2 mmol/L at rest and <6 mmol/L at peak exercise. Blood samples were collected from the central venous catheter.

Statistical analysis of the obtained data was performed using Statistica 10.0 software. The data are presented as the medians and interquartile ranges (Me [LQ; UQ]). Categorical variables are presented as the absolute values and percentages. The intergroup comparisons were made using the Mann-Whitney and Kruskal-Wallis tests for independent samples and the Friedman and Wilcoxon tests for dependent samples. Categorical variables were compared using the exact Fisher test in independent groups and the McNemar test in dependent groups. The significance of the differences in multiple groups was assumed taking into account the Holm–Bonferroni correction. Differences were considered statistically significant at $p<0.05$.

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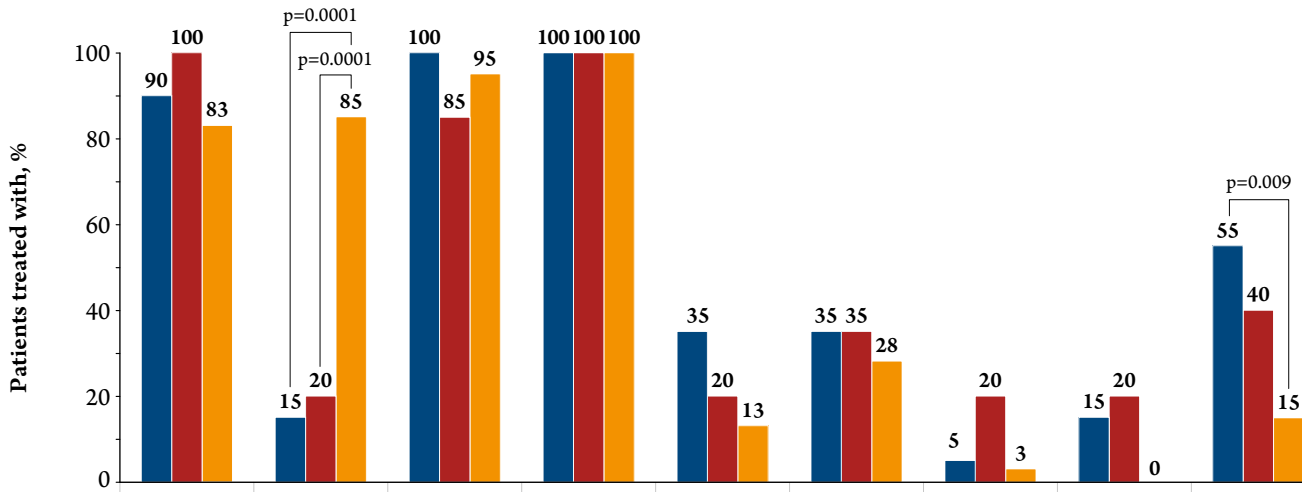
Figure 1. Drug therapy at inclusion



	Beta-blockers	ACE inhibitors/ARBs	MRAs	LDs	TDs	ICA	Digoxin	Ivabradine	Amiodarone
Group 1 (n)	36	6	40	40	14	14	2	6	22
Group 2 (n)	40	8	34	40	8	14	8	8	16
Group 3 (n)	33	34	38	40	5	11	1	0	6

ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme;
MRA, mineralocorticoid receptor antagonist; LD, loop diuretic; TD, thiazide diuretic; ICA, inhibitor of carbonic anhydrase.

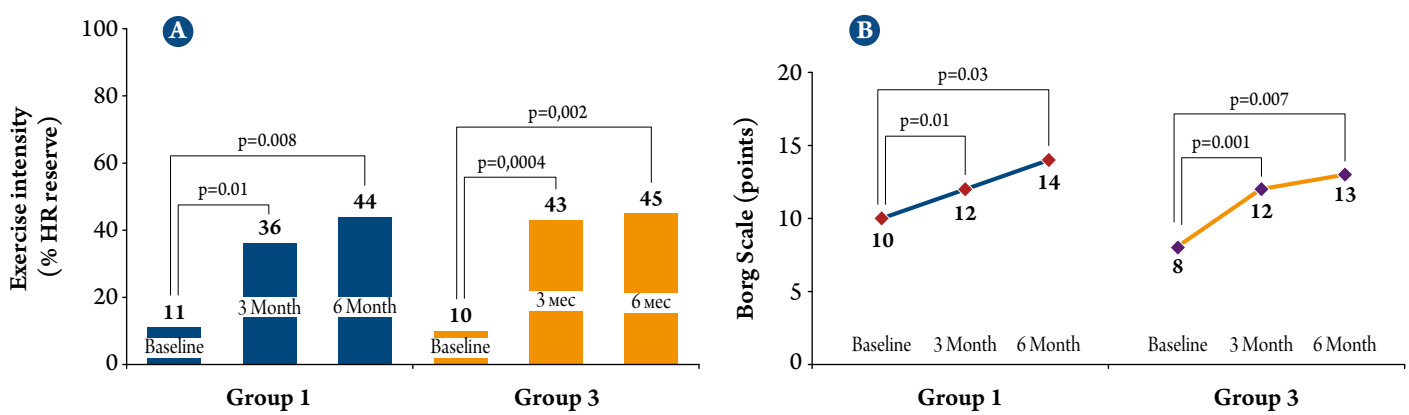
Results

Characteristics of the subjects

The age of patients was 53.5 [46.0; 57.5], 55.0 [52.0; 58.0], and 56.5 [51.0; 59.0] years, respectively, in Group 1, Group 2, and Group 3 (p>0.05). The etiology of CHF included CAD in 22 (55%), 18 (45%), and 24 (60%) patients, respectively, in Group 1, Group 2, and Group 3 (p>0.05), dilated cardiomyopathy (DCM) in 18 (45%), 22 (55%), and 16 (40%) patients, respectively (p>0.05). Prior to inclusion into study, resynchronization therapy or ICD placement was performed in 20 (50%) cases in Group 1, 15 (37.5%) patients in Group 2, and 16 (40%) patients in Group 3 (p>0.05). CHF class III was diagnosed 30 (75%), 36 (90%), and 38 (95%) patients, respectively, in Group 1, Group 2, and Group 3 (p>0.05), CHF class IV – in 10 (25%), 4 (10%), and 2 (5%) patients, respectively (p>0.05).

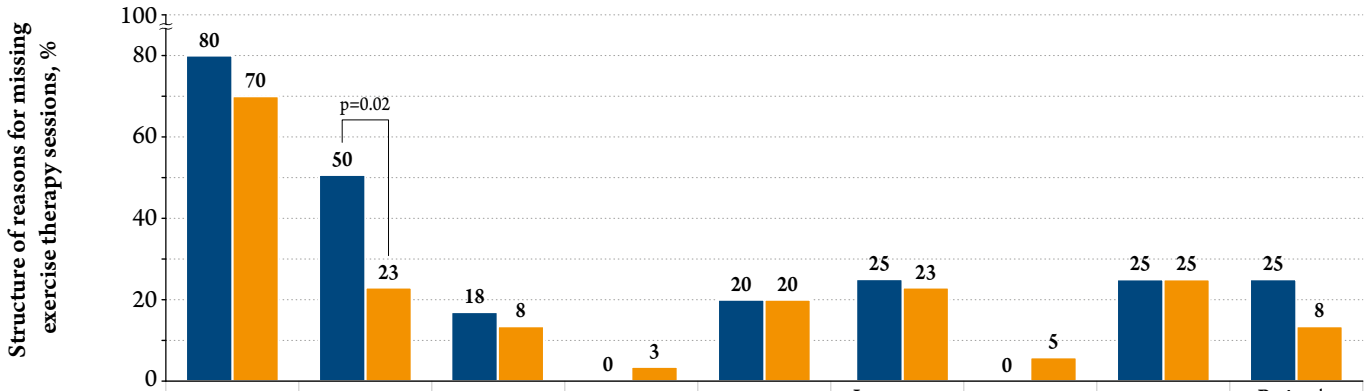
There were no statistically significant differences in the main echocardiography parameters between Groups 1, 2, and 3 at inclusion to the study: LVEF 21 [17; 29] %, 21 [17; 25] %, and 24 [18; 26] %, respectively (p>0.05); left ventricular end-diastolic volume (LVEDV) 215 [176; 270] mL, 242 [202; 287] mL, and 244 [209; 299] mL (p>0.05); left ventricular stroke volume (LVSV) 45 [36; 52] mL, 42

Figure 2. Dynamics of exercise intensity during the study



A – changes in the increase in heart rate (% of heart rate reserve); B – changes in the efforts applied to perform exercises (Borg score).

Figure 3. Structure of reasons for missing exercise therapy sessions



	Increase in CHF	Fatigue	Transfer to ICU	Angina pectoris	ARVI	Lower respiratory tract infection	AFP and AFL	Routine procedures	Patient's refusal to exercise
Group 1 (n)	32	20	7	0	8	10	0	10	10
Group 3 (n)	28	9	3	1	8	9	2	10	6

ICU, intensive care unit; AFP, atrial fibrillation paroxysm; AFL, atrial flutter; n, number of patients who missed the session.

Table 1. Causes and number of missed exercise therapy sessions

Cause	Group 1	Group 3	p
	Number of sessions		
Progression of CHF	6 [5; 10]	4 [2; 7]	>0.05
Fatigue	8 [5; 11]	4 [3; 4]	0.01
Transfer to intensive care units	4 [2; 10]	4 [1; 7]	>0.05
Angina attack	0	2 [2; 3]	>0.05
Acute respiratory viral infection	9 [7; 10]	7 [7; 8]	>0.05
Lower respiratory tract infections	14 [7; 21]	9 [7; 12]	>0.05
Paroxysms of atrial fibrillation/flutter	0	2 [2; 3]	>0.05
Treatment and diagnostic procedures	7 [4; 17]	4 [3; 9]	>0.05
Patient's refusal to exercise	5 [1; 6]	2 [2; 31]	>0.05

The data are expressed as the medians and interquartile ranges (Me [LQ; UQ]); CHF, chronic heart failure.

[37; 61] mL, and 57 [44; 75] mL (p>0.05); right ventricular (RV) contractility, tricuspid annular plane systolic excursion (TAPSE) 9 [7; 17] mm, 12 [10; 12] mm, and 14 [11; 16] mm (p>0.05); estimated pulmonary artery pressure (PAP) 45 [37; 65] mm Hg, 45 [39; 54] mm Hg, and 57 [40; 70] mm Hg (p>0.05).

Thus, inotrope-dependent patients of Group 1 and Group 2 were initially comparable in terms of main anamnestic, clinical, echocardiographic parameters, and drug therapy (Figure 1).

Dopamine or dobutamine treatment was started and discontinued according to guidelines [14–16]. The mean dopamine doses were 3.0 [2.0; 5.0] and 3.0 [2.5; 4.0] μg/kg/min in Group 1 and Group 2, respectively (p>0.05); dobutamine doses were 4.0 [3.5; 6.0] and 3.5 [3.0; 5.0] μg/kg/min, respectively (p>0.05). The baseline drug therapy is shown in Figure 1.

After 6 months, 80 (66.7%) patients completed the follow-up: 24 (60%), 22 (55%), and 34 (85%) patients from Group 1, Group 2, and Group 3, respectively (p1–3 = 0.02; p2–3 = 0.006).

During the study, 8 and 10 patients died in Group 1 and Group 2, respectively (p>0.05), in contrast to no deaths in Group 3 (p1–3 = 0.005; p^2–3 = 0.001). Heart transplantation was performed in 8, 8, and 6 patients in Group 1, Group 2, and Group 3, respectively (p>0.05).

The number of patients with episodes of CHF progression to class IV was 23 (58%), 32 (80%), and 13 (33%) in Group 1, Group 2, and Group 3, respectively (p^2–3<0.0001).

Prior to inclusion into the study, patients received inotropic therapy for 28 [16; 31] days in Group 1 and 20 [15; 22] days in Group 2 (p>0.05); its duration after inclusion in the study was 51 [37; 90] days in Group 1 and 69 [32; 104] days in Group 2 (p>0.05); and it could be canceled by

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month 6 in 24 (100%) and 15 (68%) patients in Group 1 and Group 2, respectively (p = 0.003).

Exercise intensity

Initially actual increase in HR at peak exercise was 11% and 10% of the HR reserve in Group 1 and Group 3, respectively. Patients assessed the efforts applied to perform the exercise as low intensity in Group 1 (Figure 2) and very low intensity in Group 3 (p = 0.03).

After 3 and 6 months of follow-up, there was a comparable significant increase in the exercise intensity in Group 1 and Group 3, and the efforts applied to its performance did not differ in both groups, corresponding to low-moderate intensity by month 3 and moderate intensity by month 6 of follow-up.

Distribution of therapeutic exercise routines during the study period

After 3 months of the study, TEC № 2 was applied in only 5 (15%) patients in Group 1 (p1–3>0.05); TEC № 3 – in 3 (9%) patients in Group 1 and in 7 (20%) patients in Group 3 (p>0.05); TEC № 4 – in 26 (76%) patients in Group 1 and 28 (80%) patients in Group 3 (p>0.05).

By month 6 of follow-up, TEC № 3 was used in 4 (17%) patients in Group 1 and 3 (9%) patients in Group 3 (p>0.05); and TEC № 4 – in 20 (83%) patients in Group 1 and 31 (80%) patients in Group 3 (p>0.05).

Thus, after 3 and 6 months, patients in Group 1 and Group 3 mastered the complexes of higher intensity.

Tolerance of physical rehabilitation program

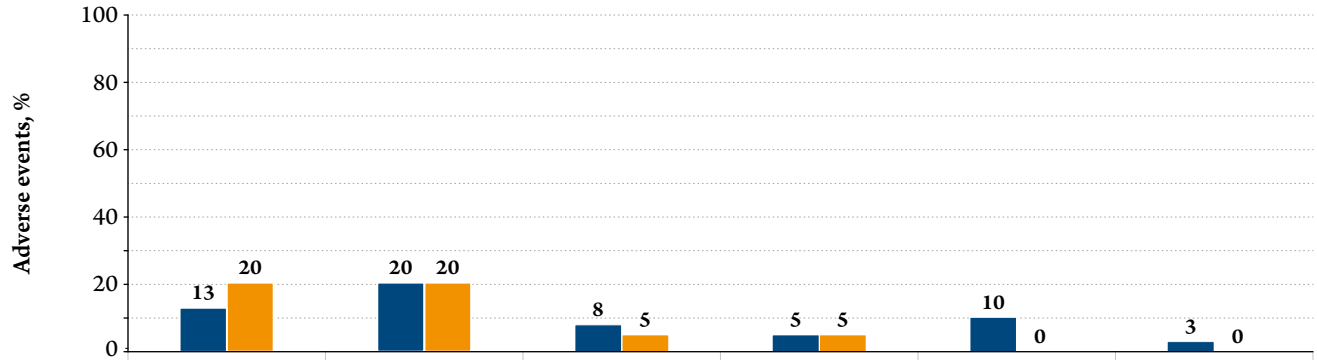
Training patients of Group 1 and Group 3 attended 88% and 92% of the scheduled sessions, respectively (p>0.05).

The structure of reasons for missing sessions and the number of patients who missed them did not differ statistically significantly, except for the number of patients and the number of missed sessions due to fatigue (Figure 3; Table 1).

Adverse events associated with exercise training

There were no cases of ACS, pulmonary edema, PE, sudden cardiac death, life-threatening rhythm disturbances,

Figure 4. Adverse events associated with exercise training



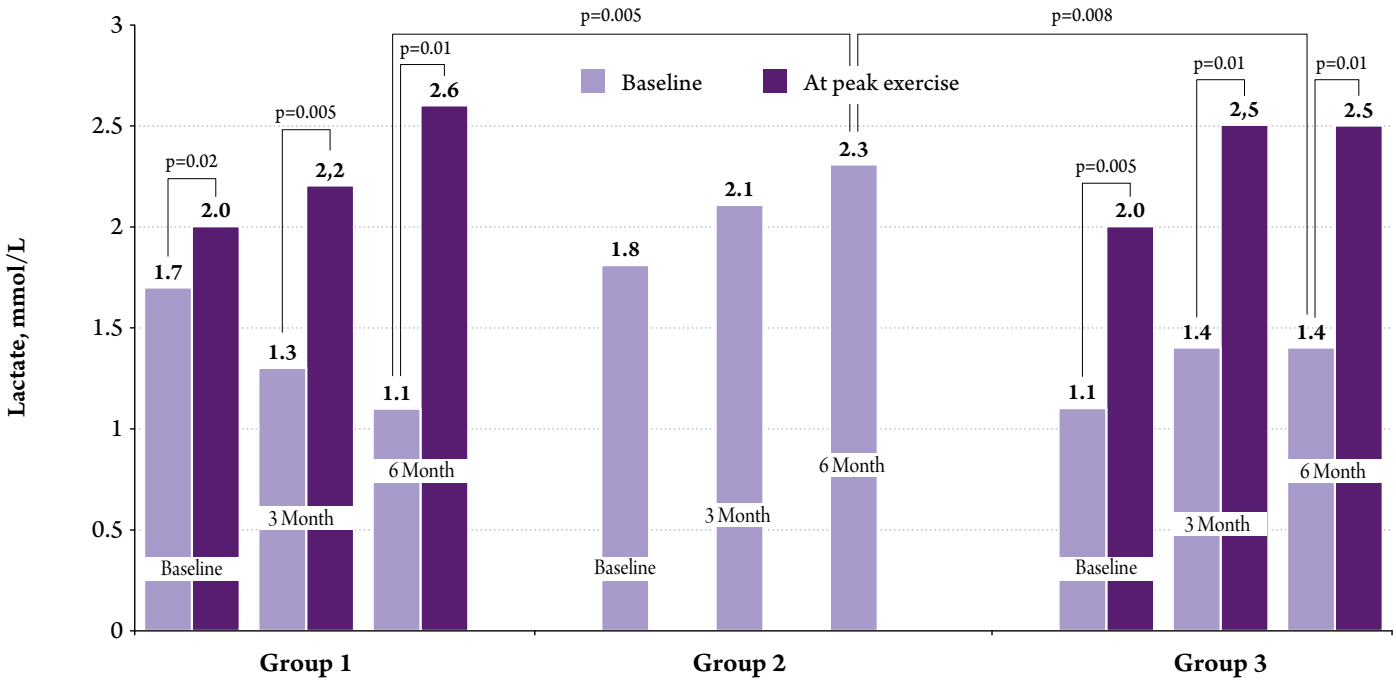
n, number of patients who missed exercise session.

Table 2. Number of sessions associated with non-fatal adverse events

Parameter	Group 1	Group 3	p
	Number of sessions		
External signs of fatigue	3 [1 ;6]	2 [1; 4]	>0.05
Dyspnea	5 [3; 6]	3 [2; 5]	>0.05
Fatigue	3 [1; 5]	2 [1; 4]	>0.05
Dizziness	2 [2; 2]	2 [1; 5]	>0.05
Angina attack	1 [1; 1]	1 [1; 1]	>0.05
Low blood pressure	1 [1; 1]	–	>0.05

The data are presented as the medians and interquartile ranges (Me [LQ; UQ]).

Figure 5. Dynamics in lactate levels at rest and at peak exercise



and ICD activation among the training patients during and 3 hours after sessions.

Non-fatal AEs occurred in a comparable number of patients in Group 1 and Group 3, and their incidence was low (Figure 4; Table 2). TEC were corrected for all patients with AEs, and they continued their participation in the PRP.

Dynamics of echocardiography Parameters

The main echocardiography parameters did not differ significantly in patients of 3 groups at all study points.

After 6 months of follow-up, there were no statistically significant changes in LVEF, LVEDV, LVSV, RV contractility, and PAP in any of the groups.

Dynamics of arterial oxygen saturation and blood lactate levels

SpO2 at rest was normal in the 3 groups and at peak exercise in Group 1 and Group 3 at baseline and at all study points.

At baseline, lactate levels at rest were normal in all groups. After 3 and 6 months, there was a tendency to a decrease in lactate levels at rest in Group 1 and a tendency to the increase in Group 2; there were no changes in Group 3. After 6 months, the lactate levels became significantly higher in patients of Group 2 compared to Group 1 and Group 3 ($p_{1-2} = 0.005$; $p^2_{-3} = 0.008$).

The levels of lactate increased statistically significantly at peak exercise compared to rest in Group 1 and Group 3. However, the mean values, despite the increase in exercise intensity, did not exceed 4 mmol/L and were not associated with clinically significant AEs throughout the study (Figure 5).

Discussion

Currently, the use of PR of inotrope-dependent patients with CHF is limited due to the lack of evidence supporting its safety and existing concerns about the increased risk of AEs during exercise and infusion of dobutamine [17] which stimulates the sympathoadrenal system, accompanied by an increase in HR, BP, myocardial O2 demand, and the associated risks of myocardial ischemia, ventricular arrhythmias (VA), and death [18, 19].

No randomized prospective studies were found to evaluate the tolerability of PA and the incidence of PA-associated AEs for patients with CHF receiving dopamine and dobutamine. Moreover, the need for inotropic therapy was an exclusion criterion in most studies [20].

The few observations including patients who required dobutamine treatment were limited to the description of several clinical cases [21, 22]. In 2018, a prospective study was published, in which high-intensity exercise was investigated in 24 patients with CHF class II–III, 12 of whom received dobutamine at a dose of 1.9 ± 0.8 μg/kg/min [23]. A major limitation of this study was lack of a control group, exclusion of patients with CHF class IV, a small sample of patients receiving catecholamines, and the lack of data on the duration of inotropic therapy. Nevertheless, all sources [22–26] pointed out good exercise tolerance, improvement in functional status, and the absence of serious AEs.

In our study, the PR algorithms recommended for patients with CHF without inotropic support [17, 27, 28]

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were adapted for inotrope-dependent patients. The developed PRP focused on exercises performed at an aerobic energy supply and included breathing exercises, exercises for small, medium, and large muscle groups, and controlled walking.

As an alternative to breathing simulators, breathing exercises using diaphragmatic and slow (without delay) breathing were used, which according to medical literature showed good tolerability and efficacy in increasing respiratory muscle strength and improving tolerance in patients with CHF without inotropic support [29].

The exercise intensity estimated by the effort applied to its performance and by the increase in HR may not coincide, therefore the determination of the exercise intensity by the actual increase in HR (in % of the individual HR reserve calculated using the Karvonen formula) has been supplemented with the estimation of the effort applied by the Borg score [11].

The recommended intensity of aerobic exercise for patients with CHF without inotropic support corresponds to 40–70% of the HR reserve with an effort applied with the Borg score of 10–14 [30].

Our study demonstrated that despite the more severe condition of patients with inotropic dependence in Group 1 compared to Group 3, patients in both groups were able to attend a comparable number of sessions (> 80% of the schedule), achieved a comparable well-tolerated moderate exercise intensity (44% and 45% of the HR reserve; the Borg score 14 and 13 in Group 1 and Group 3, respectively), which was not accompanied by clinically significant exercise-associated AEs, deterioration of echocardiographic parameters, and did not require discontinuation of participation in the PRP. It should also be noted that mortality did not differ in Group 1 and Group 2 ($p>0.05$), which indicates the safety of exercise therapy.

The obtained data are consistent with other sources that showed good tolerance and safety of exercise therapy in prognostically more favorable patients with CHF class III who have better prognosis [23, 25, 31].

A short-term increase of blood lactate level up to 5–6 mmol/L during the exercise is safe, and exercise therapy is considered optimal at its level of 2–4 mmol/L [32]. In our study, exercising patients of Group 1 and Group 3 did not have significant desaturation of arterial blood, lactate level elevation was comparable, and its values did not exceed 4 mmol/L and were not associated with clinically significant AEs [33].

The initiation of exercises, regular monitoring of their safety and evaluation of criteria for discontinuation of exercise therapy in patients included in our study were based on existing generally accepted approaches developed for patients with CHF class I–IV who do not require inotropic support. The baseline functional status, the presence or absence of signs of CHF progression and/or hemodynamic instability, prognostically unfavorable VA, hemodynamic indicators (BP and HR), and HR at rest and at the peak exercise, SpO2, the Borg scale scores, and signs of excessive fatigue were taken into account [17, 28]. Evaluation of the blood lactate levels made it possible to prove the metabolic safety of the developed PRP and minimize the risk of AEs.

The study was limited by small sample size, inotropic dependence of patients, duration of follow-up for<1 year, and inclusion of male patients only.

Conclusion

Our findings showed that a 6-month personalized physical rehabilitation program for inotrope-dependent patients with end-stage chronic heart failure, provided safety criteria are met, is well tolerated and does not increase the number of adverse events associated with chronic heart failure and physical rehabilitation. Continuous inotropic support with dopamine or dobutamine should not be considered as a contraindication to physical rehabilitation in such patients in the absence of signs of exercise intolerance and the development of life-threatening adverse events.

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