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Short-term effects of exercise training program on patients with compensated chronic heart failure

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SOUHRN

Kontext: Se srdečním selháním (heart failure, HF), což je komplexní syndrom s významnými klinickými důsledky i důsledky pro veřejné zdraví, se lze setkat přibližně u 1 % až 2 % dospělých osob. Smyslem programu pohybového tréninku při HF je zvýšit tělesnou zdatnost pacientů a zlepšit kvalitu jejich života při současném snižování pravděpodobnosti hospitalizací a úmrtí. Přes opakované zdůrazňování potřeby cvičení v doporučených postupech pro kardiorehabilitaci byla zjevná nedostatečná účast pacientů s HF v těchto programech.
Cíle: Zhodnotit, jaký dopad má krátký, strukturovaný program pohybového tréninku na jedince s kompenzovaným chronickým srdečním selháním ve smyslu zlepšení hodnot klinických, laboratorních a echokardiografických parametrů.
Metody: Randomizované kontrolované studie se zúčastnilo 107 ambulantních pacientů s chronickým srdečním selháním (HFrEF a HFmrEF) v klinicky stabilizovaném stavu. V období od května 2022 do června 2023 byli účastníci studie zařazováni buď do skupiny s cvičením, nebo do kontrolní skupiny.
Intervence: Obvyklá péče plus aerobní pohybový trénink po dobu 12 týdnů.
Shromažďovaly se hodnoty 6MWT, KCCQ-12, krevní vzorky pro rutinní laboratorní vyšetření a hodnoty NT-proBNP v séru; při vstupu do studie a po 12 týdnech bylo provedeno klasické echokardiografické vyšetření a vyšetření metodou dvourozměrného „speckle tracking" (2D-speckle tracking); rovněž se zaznamenávaly nežádoucí příhody včetně úmrtí z kardiovaskulárních příčin, převozu na oddělení urgentního příjmu (ER) a hospitalizace po 12 týdnech.
Výsledky: Pacienti byli náhodně zařazováni do skupiny s cvičením (n = 60) nebo do kontrolní skupiny (n = 47). V obou skupinách převažovali muži, 58 % účastníků ve skupině s cvičením a 68 % účastníků v kontrolní skupině mělo ischemickou etiologii.
Při celkové adherenci k programu pohybového tréninku 83,7 % absolvovalo 58 účastníků (96,7 %) kontinuální pohybový trénink, zatímco ostatní účastníci absolvovali vysoce intenzivní intervalový trénink.
Náš výzkum prokázal, že u skupiny s cvičením se statisticky významně zvýšila funkční kapacita v podobě prodloužené vzdálenosti v testu 6MWT (420 vs 260 m; $p \leq 0{,}001$) a VO_{2max} (16,8 vs 14,7 ml/kg/min; $p \leq 0{,}001$); navíc bylo v dotazníku KCCQ-12 zaznamenáno zlepšení kvality života o 8 bodů v srovnání s kontrolní skupinou ($p \leq 0{,}001$).
U skupiny s cvičením bylo ve srovnání s kontrolní skupinou pozorováno i statisticky významné zlepšení u globální longitudinální deformace (–12,5 vs. –9,7 %; $p = 0{,}005$) a ejekční frakce (37,8 vs. 33,1 %; $p = 0{,}04$).
Během sledování byl nalezen statisticky nevýznamný rozdíl v hodnotách NT-proBNP mezi oběma skupinami. Ve skupině s cvičením bylo hospitalizováno méně pacientů než v kontrolní skupině; tento rozdíl byl statisticky významný ($p = 0{,}045$). Incidence ostatních příhod byla v obou skupinách srovnatelná.
U skupiny s cvičením bylo v hodnotách 6MWT, VO_{2max} ($p \leq 0{,}001$), NT-proBNP ($p = 0{,}05$), snížené srdeční frekvence ($p = 0{,}005$), snížené ejekční frakce LK na konci diastoly ($p = 0{,}007$), sníženého objemu na konci systoly ($p \leq 0{,}001$) a zlepšené ejekční frakce ($p \leq 0{,}001$) zaznamenáno statisticky významné zlepšení při srovnání vstupních hodnot a hodnot na konci sledování.
Závěry: Pravidelně cvičící účastníci s chronickým srdečním selháním uvedli zlepšení ejekční frakce, zvýšení kvality života a funkční kapacity a nižší incidenci nežádoucích příhod včetně počtu hospitalizací.

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ABSTRACT

Background: About 1% to 2% of adults suffer from heart failure (HF), a complex syndrome with significant clinical and public health issues. Exercise training for heart failure seeks to enhance patients' physical fitness and quality of life while simultaneously diminishing the likelihood of hospitalizations and mortality. Poor heart failure patient participation was apparent despite strong guidelines for cardiac rehabilitation.

Objectives: For evaluating how a brief, structured exercise training program impacts those suffering from compensated chronic heart failure in terms of improving clinical, laboratory, and echocardiographic parameters.

Methods: 107 medically stable outpatients with chronic heart failure (HFrEF and HFmrEF) participated in a randomized control trial. Participants were allocated to either the exercise or control groups between May 2022 and June 2023.

Intervention: usual care plus aerobic exercise training for 12 weeks.

6MWT, KCCQ-12, blood samples for routine labs and serum NT-proBNP were collected and conventional echocardiography and 2D-speckle tracking studies were done at baseline and after 12 weeks, the adverse events after 12 weeks were recorded including cardiovascular death, ER visits and hospitalization.

Results: Exercise group (n = 60) and control group (n = 47) were allocated at random to the patients.

Both groups were dominated by males, and 58% of the exercise group and 68% of the control group had ischemic etiology. With the overall adherence to the exercise training program being 83.7%, the 58 exercise group patients (96.7%) underwent continuous exercise training while the rest underwent high intensity interval training.

Our research revealed that the exercise group significantly improved their functional capacity by increasing their 6MWT distance (420 vs 260 m, $p \leq 0.001$) and VO_{2max} (16.8 vs 14.7 ml/kg/min, $p \leq 0.001$), additionally their quality of life by 8 points on the KCCQ-12 when compared to the control group ($p \leq 0.001$).

The exercise group's global longitudinal strain (–12.5 vs. –9.7%, $p = 0.005$) and ejection fraction (37.8 vs. 33.1%, $p = 0.04$) both significantly improved when in comparison to the control group.

At the follow-up, there was insignificant difference in the NT-proBNP between the two groups.

The exercise group experienced fewer hospitalized patients than the control group, which was statistically significant ($p = 0.045$). Other adverse events were comparable in both groups.

6MWT, VO_{2max} ($p \leq 0.001$), NT-proBNP levels ($p = 0.05$), decreased heart rate ($p = 0.005$), decreased LV end--diastolic ($p = 0.007$), end-systolic volumes ($p \leq 0.001$), and improved ejection fraction ($p \leq 0.001$) were all significantly improved when comparing baseline and follow-up data of the exercise group.

Conclusions: Regular exercisers with chronic heart failure report improving ejection fraction, quality of life, functional capacity, and fewer adverse events, encompassing hospitalization as well.

Keywords:
Exercise training
Heart failure
6MWT

Background

Heart failure (HF) is a complex clinical syndrome with several signs and comorbidities,[1] continues to be a significant health problem that impacts 1% to 2% of humans.[2] Due to a population that is increasing in age, the prevalence of heart failure continues to increase,[3] decreasing the quality of life[4] and raising the financial strain on the public healthcare system and patients.[5]

Over the past three decades, cardiac rehabilitation has transformed from a sole emphasis on exercise training to a comprehensive, multidisciplinary approach. It now encompasses patient evaluation, education, risk factor management comprising dietary guidance and lifestyle changes – smoking cessation support, psychological care, and strategies to address adherence challenges.[6,7]

Improving a patient's capacity for physical activity and overall health-related well-being, as well as enhancing the effects of medications and devices in lowering the risk of death and hospital stay, are the main goals of exercise training for heart failure.[6–8]

Cardiac rehabilitation aims to help patients reach goals for controlling coexisting conditions, such as psychological disorders, musculoskeletal limitations, and sleep apnea; adhere to guidelines for medical therapies; and achieve cardiovascular health and guidelines for controlling blood pressure, lipids, weight, blood glucose, and tobacco exposure.[9]

In the last ten years, evidence from numerous meta-analyses has highlighted the advantages of exercise training for heart failure, comprising a relative reduction in hospitalizations for both heart failure, all cause cardiovascular events and better health-related quality of life outcomes.[10,11]

Findings from research employing safe exercise regimens support the idea that heart failure patients can benefit from activity-based rehabilitation. The studies encompassed in the systematic review and meta-analyses reported no significant adverse effects linked to exercise training.[10–12]

Despite strong recommendations in the ESC[1] 2021 and AHA[13] 2022 heart failure guidelines for cardiac rehabilitation. There was a clear lack of involvement from heart failure patients, which has been linked to several important contributing factors involving patients, healthcare providers, and systemic problems.[6]

This study's objective is assessing how a brief, structured exercise training program can enhance clinical, laboratory, and echocardiographic parameters in patients with compensated chronic heart failure.

Methods

Study design and patients' selection

This was a randomized controlled interventional study which included 107 patients presented with chronic sta-

ble heart failure (NYHA I–III) to Kasr Al Ainy specialized heart failure clinic in the period from May 2022 to June 2023

Inclusion criteria

Patients with compensated heart failure who had a reduced or mildly reduced ejection fraction (EF <50%) were recruited for the study.

Exclusion criteria

Exclusion criteria comprised recent acute coronary syndrome patients, untreated life-threatening cardiac arrhythmias, atrial fibrillation, significant primary valvular abnormalities, patients with prosthetic valves, high degree atrioventricular block, pregnancy, acute myocarditis and/or pericarditis, severe hypertrophic obstructive cardiomyopathy with the resting or provoked LVOT gradient >50 mmHg, intracardiac thrombi, history of significant myocardial ischemia or arrhythmia during low-intensity exercise, acute systemic illness or fever, cerebrovascular or musculoskeletal disease preventing exercise testing or training, severe chronic obstructive pulmonary disease, poor echocardiographic window 'low patients' adherence in the exercise group (defined as non-adherent <20% and partially adherent patients [20–80%]) and consent refusal.

Ethical committee approval

On August 4, 2022, the Cairo University Faculty of Medicine's local ethics committee approved the study protocol, which was assigned the code MD-214-2022.

Patients' consent

All patients signed an informed consent after explaining the study protocol and they approved on publication of study results.

Randomization

Heart failure patients were randomized through asking them to choose a number; either 1 or 2, where 1 was assigned to the exercise group and 2 was assigned to the control group. All patients were on optimal treatment for heart failure including diuretics, maximally tolerated doses of RAAS blockers (angiotensin receptor/neprilysin inhibitor [ARNI], angiotensin receptor blockers [ARBs], angiotensin-converting enzyme [ACE] inhibitors, mineralocorticoid receptor antagonist [MRA], sodium-glucose cotransporter-2 [SGLT2] and beta-blockers [BB]) in accordance with the latest recommendations of the European Society of Cardiology guidelines for HF treatment.[1]

Baseline assessment

Clinical assessment and ECG

Detailed history was taken including heart failure aetiology and cardiovascular risk factors. Thorough physical examination was performed including assessment of heart failure signs, blood pressure, heart rate and weight measurement.

Electrocardiogram (ECG)

A twelve lead ECG was performed to detect any form of arrhythmias and to assess ECG waves morphology and durations.

Echocardiography

The American Society of Echocardiography's (ASE) guidelines for adult cardiac chamber quantification were followed in all measurements.[14,15]

The following were detected utilizing two-dimensional, M mode, and Doppler techniques: left ventricular (LV) internal dimensions and ejection fraction using the biplane Simpson's method; left atrial diameter; tricuspid annular plane systolic excursion (TAPSE); tissue Doppler-derived right ventricular systolic excursion velocity S'; estimated pulmonary artery systolic pressure (EPASP); and left ventricular diastolic function (mitral inflow E and A-wave velocities, and e' using TDI at the lateral and medial mitral annuli. The average E/e ratio was computed automatically.

Echocardiography with speckle tracking

Acquiring images: To ensure that the endocardial border could be seen clearly and without foreshortening, three typical apical images were carefully taken. The frame rate was set above 60 frames per second by appropriately adjusting the gain, depth, and sector width.

Analysis of images: Clips of four cardiac cycles of the apical four chamber view, apical two chamber view, and apical three chamber view were recorded and examined either offline or during the study using the Cardiac Motion Quantification (CMQ) tool on the Q lab10 program (Philips' ultrasonography). First, the end-systole was defined using the aortic valve closure (AVC) in the apical three-chamber view. Three locations at the end diastolic frame were identified then to determine the region of interest (ROI): two mitral annular points low and within the myocardium at the level of mitral valve insertion, and one apical point at the endocardial border of the apex.

The program automatically tracked the internal (endocardial) and external (epicardial) borders during the heart cycle. The operator manually modified the tracking to ensure high-quality tracking. The longitudinal deformation characteristics were automatically converted into graphical and numerical displays for each segment from each view. The same procedure was applied to the apical 4-chamber and apical 2-chamber views using the same sequence. The average strain from the three apical images was automatically used to compute the LV global longitudinal strain (GLS).

Venous blood sampling

NT-proBNP plasma level was tested on presentation using standard venepuncture techniques. Prior to centrifugation, the collected material was left to coagulate for 30 minutes. Blood serum was then isolated and stored at –70 °C until analysis. Serum levels of NT-proBNP were measured using the enzyme-linked immunoassay (ELISA) technique.

Six-minute walk test

Participants received instructions to walk as far as they could in six minutes on a 30-meter course, receiving standardized encouragement and rest periods as needed. The maximum heart rate attained and the total distance walked in six minutes while at rest were recorded.

Quality of life questionnaires

Utilizing the Kansas City Cardiomyopathy Questionnaire, quality of life was assessed.[16]

Exercise training program

Exercise group were subjected to pre-planned exercise program, which consisted of supervised sessions in hospital (the exercise training was held at the Cardiology department of the tertiary care center) and home-based sessions, where patients performed exercise at home.

Endurance aerobic exercise training in the form of treadmill exercise (continuous or interval training) was used for supervised session 2 to 3 times a week for a minimum of 12 sessions with full compliance to transform to a home based one and a total of 36 sessions for a fully supervised program. While for home-based sessions; patients were advised to do certain exercises as marching on the spot, sit to stand and shadow boxing [(1)]. Patients were given a booklet with illustrated figures of exercises after explanation of the exercises in the clinic during the supervised sessions and they were given a logbook for writing the number and duration of sessions.

Intervals of training in order to enable the patient to engage in extended training sessions, continuous training is often carried out at moderate exercise intensities under steady-state aerobic energy yield circumstances. Starting low and moving slowly is recommended for patients who are more deconditioned (i.e. at low intensity for 5–10 min twice a week). At low or no workload, the patient is instructed to alternate short (10–30 s) bursts of moderate–high intensity (50–100% peak exercise capacity) activity with a prolonged rest (80–60 s) phase. If well tolerated, the time of each training session is raised initially, and then the number of sessions per day.

Each exercise training was preceded by a warmup period and was followed by a cool down period each lasted for 5-minutes.

By calculating the heart rate ratio method and taking a percentage of the maximum oxygen consumption (VO_{2max}), which was measured during the 6MWT, the intensity of exercise training was established {12.1(HR_{max}÷ $HR_{resting}$)}.[18]

Patients were transitioned from a medically supervised program to a home based one, after at least four weeks of supervised sessions.

Patients were followed by intermittent supervised sessions at least once per week and by regular phone calls once weekly to enhance compliance and to inform them about the next supervised session timing.

Follow-up at the end of the study

After 3 months of enrollment, both groups were called back for follow-up clinical data, 6MWT, NT pro BNP, echocardiography and KCCQ-12.

Clinical events

Clinical events included hospitalization (defined as clinical decompensation of previously stabilized HF judged to indicate intravenous HF therapies), cardiovascular death, and emergency room visits (defined as a constellation of signs, symptoms, diagnostic testing, and HF-directed therapy).

Primary outcomes

Change in six-minute walk test, NT pro-BNP levels, LV global longitudinal strain and clinical follow-up including blood pressure and heart rate after successful rehabilitation period.

Secondary outcomes

- Change in the quality of life (using KCCQ-12) after successful rehabilitation.
- Hospitalization and mortality within the study period.
- Compliance to scheduled visits and to anti-failure drugs.
- Need for muscle relaxants during the study period.

Statistical analysis

Statistical analysis was executed utilizing SPSS 26 edition. Quantitative variables were expressed as mean and standard deviation. Comparing means among groups was estimated utilizing independent samples Student t-test whereas comparison between means at baseline and after rehabilitation was done utilizing paired samples Student t-test. Qualitative variables were presented as frequency and percentages. Chi square/Fischer Exact test was used for comparing qualitative variables in the 2 study groups. Analysis was carried out to estimate the predictability of GLS, EF, KCCQ-12 and 6-minute walking distance for improvement. A p-value <0.05 was deemed significant.

Results

The 107 heart failure patients in the study were split into two groups: the exercise training group (n = 60) and the control group (n = 47) (**Fig. 1**).

Baseline clinical and echocardiographic data

The baseline demographic data showed male predominance in both groups with older age in the control group. The heart failure duration was longer in the control group, ischemic cardiomyopathy was comparable in both groups, and PCI was the most common procedure in both groups (**Table 1**).

Patients allocated to the exercise group walked a statistically greater baseline distance than those in the control group. Even so, as listed in **Table 1**, there were insignificant differences across the two groups in the KCCQ-12 questionnaire, resting or maximum heart rate attained during the test, or VO_{2max}.

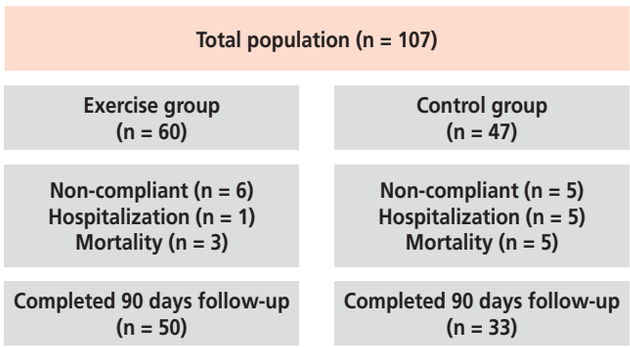


Fig. 1 – Flow diagram showing inclusion of patients

Table 1 – Baseline clinical and laboratory assessment

	Exercise group N = 60	Control group N = 47	*p*-value
	No. (%)	No. (%)	
Age, years (mean ± SD)	50.8 ± 10.5	57.0 ± 11.0	0.003
Sex, male	52 (86.5)	38 (81)	0.414
Diabetes	20 (33.3)	22 (47)	0.157
Hypertension	16 (26.5)	19 (40.5)	0.132
Smoking	29(48)	25 (53)	0.618
Dyslipidaemia	1 (1.7)	4 (8.5)	0.096
Coronary artery disease	34 (56.5)	32 (68)	0.228
DCM	25 (41.7)	15 (32)	0.301
ICM	35 (58.3)	32 (68)	0.30
LBBB morphology	9 (15)	7 (15)	0.605
PCI	29 (48.3)	29 (61.7)	0.168
CABG	2 (3.3)	0 (0)	0.206
	Mean ± SD	**Mean ± SD**	
Systolic BP	112 ± 20	113.5 ± 18.5	0.70
Diastolic BP	71 ± 12.5	70.4 ± 11.4	0.79
Heart rate	80.5 ± 15.5	82.7 ± 13.2	0.426
Weight (kg)	79.7 ± 15.2	78.3 ± 13	0.62
6MWT			
Distance (m)	304 ± 75.0	265 ± 40.0	0.001
Resting heart rate	82.1 ± 15.9	82.3 ± 13.5	0.957
Max. heart rate	100.8 ± 18	100 ± 16	0.840
SO_2 (%)	97.2 ± 1.5	96.8 ± 1.2	0.126
Rests (N, %)	31(51.7)	33 (70)	0.134
VO_{2max} (ml/kg/min)	15 ± 1.6	14.7 ± 1.5	0.380
KCCQ-12 score	55 ± 10.5	52.5 ± 8.0	0.166
NT Pro-BNP (pg/ml)	5574.9 ± 5468.6	3880.7 ± 4485.5	0.091

CABG – coronary artery bypass graft; DCM – dilated cardiomyopathy; ICM – ischemic cardiomyopathy; KCCQ-12 – Kansas City Cardiomyopathy Questionnaire; NT-proBNP – N-terminal pro-B-type natriuretic peptide; PCI – percutaneous coronary intervention, SO_2 – oxygen saturation ,VO_{2max} – maximal oxygen consumption; 6MWT – six-minute walk test.

Both groups showed comparable baseline echocardiographic results except for the GLS which was better in patients assigned to the exercise group (**Table 2**).

Exercise training

Among the exercise group 58 patients (96.7%) underwent continuous exercise training while the rest underwent high intensity interval training.

Regarding the frequency of the exercise 66.7% of the exercise group with lower functional capacity trained two times per week while the rest trained three times per week as shown in **Table 3**.

The starting exercise duration was 7 minutes with a workload of 10.5 watts with a maximum exercise duration reaching 16.6 minutes with a maximum workload of 51.5 watts.

The adherence to the exercise training program was 83.7%.

Follow-up clinical and echocardiographic data

Clinical data, comprising blood pressure, heart rate, and weight, did not significantly vary between the two groups at the follow-up. Nevertheless, the exercise group's 6MWT was significantly longer than the control groups, with fewer rests during the test and a higher VO_{2max}, as indicated in **Table 4**.

Regarding the symptoms we used the KCCQ-12 as that contains four subdomains: Physical limitation, Symptom frequency, Quality of life, and Social limitations which include fatigue, shortness of breath and edema as a marker for symptom improvement and it shows a significant improvement in these symptoms in the exercise group compared to the control one..

Also, we can see that quality-of-life parameters 'feelings of being disabled and self-assessment of general well-being' were positively affected by the exercise training.

Moreover, the follow-up NT-proBNP results indicated insignificant differences.

Table 2 – Baseline echocardiographic data

	Exercise group	Control group	*p*-value
	Mean ± SD	Mean ± SD	
LVEDD (mm)	56.5 ± 8.0	56 ± 7.0	0.678
LVESD (mm)	47.6 ± 9.0	46 ± 7.4	0.293
EDV (ml)	174.6 ± 52.3	170.6 ± 44.8	0.677
ESV (ml)	117.2 ± 48.5	115.4 ± 39.3	0.829
Ejection fraction (%)	34.2 ± 9.0	32.5 ± 8.6	0.331
E/A ratio	1.6 ± 1.0	1.5 ± 1.0	0.706
E/e' medial	15.1 ± 6.5	14.5 ± 6.7	0.591
E/e' lateral	10.0 ± 4.0	10.2 ± 4.5	0.836
E/e'	12.55 ± 5.2	12.35 ± 5.6	0.71
TAPSE (mm)	18.4 ± 4.4	16.8 ± 4.2	0.068
S-wave velocity of tricuspid annulus (cm/s)	11.1 ± 2.6	10.1 ± 2.8	0.078
EPASP (mmHg)	29 ± 15	32 ± 16	0.332
Moderate mitral regurgitation (No. %)	12 (20)	15 (31.9)	0.226
Severe mitral regurgitation (No. %)	8 (13.3)	5 (10.6)	
GLS (%)	–11.2 ± 3.8	–9.4 ± 4.0	0.017

EDV – end-diastolic volume; EPASP – estimated pulmonary artery systolic pressure; ESV – end-systolic volume; GLS – global longitudinal strain; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end systolic diameter; TAPSE – tricuspid annular plane systolic excursion.

Table 3 – Details of exercise training program

Exercise training	**Exercise group N = 60**
	No. (%)
Type	
Continuous training	58 (96.7)
High intensity interval training	2 (3.3)
Frequency	
Twice/week	40 (66.7)
Three times/week	20 (33.3)
Duration	
Starting duration (mins)	7.0 ± 2.4
Maximum duration (mins)	16.5 ± 4.3
Workload	
Starting workload (watts)	10.5 ± 1.1
Maximum workload (watts)	51.5 ± 33.9
Adherence (%)	83.7 ± 12.2

At the follow-up, the exercise group's global longitudinal strain and ejection fraction were greater than those of the control group (**Table 5**).

Clinical events

The exercise group had a decreased rate of hospitalization compared to control group (n = 1, 1.7% vs n = 5, 10.6%, p = 0.045). Also, the exercise group had a numerically decreased rate of mortality and ER visits as compared to control group as shown in **Table 6**.

The exercise group had lower rate of hospitalization (n = 1, 1.7% vs n = 5, 10.6%, p = 0.045).

The only hospitalized patient in the exercise group was a fifty-seven-year-old male with ICM with acute decompensated heart failure after 8 weeks of exercise training. This patient was non-compliant to his medications for a week prior to hospitalization, and he stopped his exercise training after being discharged.

Whereas the hospitalized participants in the control group all were admitted with acute decompensation; one of them the precipitating factor was cellulitis and was admitted at the Cardiology ward after three follow-up visits over six weeks. In another patient the precipitating factor was chest infection and was enrolled to the CCU after 4 follow-up visits over 2 months.

Of the three patients that remained, two got admitted to the hospital with acute decompensated HF mainly with manifestations of right-sided heart failure at the Cardiology ward after 4 and 6 weeks of follow-up respectively, while the last patient was admitted with biventricular failure after 2 follow-up visits over 1 month.

Moreover, the exercise group had lesser rate of mortality and ER visits as opposed to the control group but none of them were significant.

Regarding the mortality in the exercise group the first patient was a fifty-three-year-old male patient with DCM who was admitted to the CCU with cardiogenic shock that was irreversible despite inotropic support and vasopressors and arrested after 2 days from admission. He was on his 9th week of the exercise training program, and he was compliant on it and was on loop diuretics, ACE-I, BB and MRAs and

Table 4 – Follow-up clinical, 6MWT, KCCQ-12 and laboratory data

	Exercise group	Control group	*p*-value
	Mean ± SD	Mean ± SD	
Systolic BP (mmHg)	116.4 ± 18.4	116.8 ± 22.8	0.928
Diastolic BP (mmHg)	71.9 ± 12	72.8 ± 12	0.751
Heart rate	73.5 ± 12.9	79.2 ± 14.3	0.061
Weight (Kg)	77.6 ± 15	79.1 ± 12.6	0.650
6MWT			
Distance (m)	420.4 ± 102	260 ± 55.8	≤0.001
Resting heart rate	73.4 ± 12.8	79.2 ± 14.3	0.06
Max heart rate	101.2 ± 18.2	96.1 ± 17	0.211
Rests	5 (8.3)	15 (32)	≤0.001
VO_{2max}(ml/kg/min)	16.8 ± 2.4	14.7 ± 1.3	≤0.001
KCCQ-12 score	61.7 ± 10.1	53.1 ± 8.3	**≤0.001**
NT-proBNP (pg/ml)	4330 ± 4418.7	4156 ± 6348.4	0.883

KCCQ-12– Kansas City Cardiomyopathy Questionnaire; NT-proBNP – N-terminal pro-B-type natriuretic peptide;VO_{2max} – maximal oxygen consumption; 6MWT – six-minute walk test.

Table 5 – Follow-up echocardiography

	Exercise group	Control group	*p*-value
	Mean ± SD	Mean ± SD	
LVEDD (mm)	54.1 ± 7.4	55.1 ± 7.2	0.596
LVESD (mm)	43.4 ± 8.8	44.6 ± 7.7	0.540
EDV (ml)	162 ± 58	164.6 ± 44.9	0.847
ESV (ml)	102.4 ± 50	111.1 ± 37.5	0.417
Ejection fraction (%)	37.8 ± 10	33.1 ± 9.0	0.040
E/A	1.4 ± 0.9	1.26 ± 0.62	0.417
E/E' medial	12.9 ± 6.5	14.4 ± 6.1	0.335
E/E' lateral	10.6 ± 15.5	9.8 ± 4.5	0.784
E/e'	11.75 ± 11.0	12.1 ± 5.3	0.559
TAPSE (mm)	19.5 ± 4.6	17.5 ± 4.3	0.057
S' velocity (cm/s)	11.7 ± 2.8	10.4 ± 2.6	0.057
EPASP (mmHg)	27 ± 15	34.5 ± 18.6	0.060
Moderate mitral regurgitation (N, %)	5	10	0.048
Severe mitral regurgitation (N, %)	7	3	
GLS (%)	–12.5 ± 4	–9.7 ± 4.2	0.005

EDV – end-diastolic volume; EPASP – estimated pulmonary artery systolic pressure; ESV – end-systolic volume; GLS – global longitudinal strain; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; TAPSE – tricuspid annular plane systolic excursion.

of LBBB morphology and had depression. The other patient was forty-five years old and entered the hospital with cardiogenic shock, and he had history of previous admission with cardiogenic shock 6 months prior to mortality. He was on his 4th week of the exercise training program.

Whereas the third patient was forty-five-year-old male patient presented with ICM, and it was because of sudden cardiac death after 3 weeks of the exercise training at home.

In the control group, two patients were admitted and died in other hospitals, the first one was a 60-year-old male who was admitted with acute decompensated heart failure precipitated by cellulitis and worsening of renal function (his baseline creatinine was 1.7 mg/dl) and was on loop and thiazide diuretics. He was not taking his beta-blockers due to borderline blood pressure. The second patient was a seventy-year-old female patient who entered the hospital with acute decompensated heart

Table 6 – Clinical events during the follow up period

	Exercise group N = 60	Control group N = 47	P value
	No. (%)	No. (%)	
Hospitalization	1 (1.7)	5 (10.6)	0.045
Emergency department visits	10 (16.7)	13 (27.7)	0.170
Mortality	3 (5)	5 (10.6)	0.271

Table 7 – Paired comparison in exercise and control group

	Exercise group Baseline	Exercise group Follow-up	*p*-value	Control group Baseline	Control group Follow-up	*p*-value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Systolic BP (mmHg)	114 ± 20.5	116.4 ± 18.4	0.312	113 ± 18.3	116.8 ± 22.7	0.235
Diastolic BP (mmHg)	71.7 ± 12.5	72 ± 11.9	0.871	70.6 ± 11.4	72.8 ± 12.0	0.263
Heart rate	79.5 ± 15.8	73.5 ± 12.6	0.005	81.2 ± 14.2	79.2 ± 14.2	0.334
Weight (Kg)	79.7±15.2	77.6 ± 15	**0.035**	79.0 ± 13.0	79.1 ± 12.6	0.883
6MWT						
Distance (m)	312 ± 75	420 ± 102	≤0.001	267.5 ± 40.4	260 ± 55.8	0.202
Resting heart rate	81.6 ± 16.6	73.5 ± 12.8	≤0.001	81.2 ± 14.2	79.2 ± 14.2	0.334
Max. heart rate	100.3 ± 19	101.3 ± 18.2	0.672	100 ± 15.8	96.2 ± 17.0	0.075
Rests	31 (51.7)	5.0 (8.3)				
VO_{2max} (ml/kg/min)	15.0 ± 1.6	16.8 ± 2.4	**≤0.001**	14.9 ±1.6	14.7±1.3	0.239
KCCQ-12 score	55.4 ± 10.5	61.7 ± 10.1	≤0.001	54.2 ± 7.2	53.1 ± 8.3	0.039
NT pro-BNP (pg/ml)	6140.7 ± 6858.5	4330 ± 4418.7	0.054	3887.9 ± 3712.7	4156.0 ± 6348.4	0.835
LVEDD (mm)	55.96 ± 7.7	55.1 ± 7.2	0.007	55.3 ± 7.7	55.1 ± 7.4	0.757
LVESD (mm)	45.3 ± 8.1	44.6 ± 7.7	≤0.001	46.9 ± 8.7	43.4 ± 8.7	0.207
EDV (ml)	164.9 ± 42.8	162.1 ± 58	0.026	164.9 ± 42.8	164.6 ± 44.8	0.949
ESV (ml)	114.1 ± 49.4	102 ± 50.6	0.003	107.6 ± 33.5	111.1 ± 37.5	0.432
EF (%)	35.2 ± 9.1	37.8 ± 10	≤0.001	34.2 ± 8.3	33.1 ± 8.9	0.180
Left atrial diameter (mm)	40.6 ± 7.8	41.5 ± 5.1	0.264	43.4 ± 5.2	41.9 ± 8.8	0.286
E/A	1.5 ± 1.0	1.4 ± 0.9	0.351	1.3 ± 0.8	1.2 ± 0.6	0.534
E/E' medial	14.4±6.7	12.9±6.5	0.053	14.8 ± 7.4	14.4 ± 6.1	0.593
E/E' lateral	9.3±3.9	10.6±15.5	0.551	10.1 ± 4.6	9.8 ± 4.5	0.648
E/e'	11.85±5.3	11.75±11.0	0.302	12.45 ± 6.0	12.1 ± 5.30.6205	0.620
TAPSE (mm)	18.7±4.2	19.5±4.6	0.103	17.3 ± 4.1	17.4 ± 4.3	0.758
S' velocity (cm/s)	11.5±2.6	11.7±2.8	0.620	10.5 ± 2.7	10.4 ± 2.7	0.833
GLS (%)	-11.9±3.6	-12.5±3.9	0.052	-9.8 ± 3.8	-9.7 ± 4.1	0.892

EDV – end-diastolic volume; EPASP – estimated pulmonary artery systolic pressure; ESV – end-systolic volume; GLS – global longitudinal strain; KCCQ-12 – Kansas City Cardiomyopathy Questionnaire; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end--systolic diameter; NT-proBNP – N-terminal pro-B-type natriuretic peptide; TAPSE – tricuspid annular plane systolic excursion; VO_{2max} – maximal oxygen consumption; 6MWT – six-minute walk test.

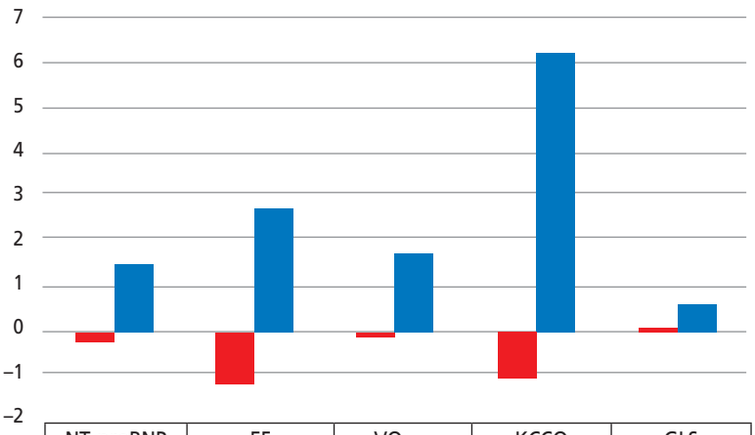
failure while she was on full guideline directed medical therapy. She had a history of mastectomy 20 years ago with completed chemotherapy sessions.

Two other patients had sudden cardiac death at their homes after one month of follow-up while another one had sudden cardiac death at home after two months of follow-up.

The ER visits were all due to volume overload symptoms.

Paired comparison in exercise and control group

When comparing baseline to follow-up data of the exercise group there was significant enhancement in 6MWT, VO_{2max}, NT-proBNP levels, lower heart rate, reduction in



	NT-proBNP	EF	VO_{2max}	KCCQ	GLS
Control group	–0.27	–1.2	–0.2	–1.1	–0.05
Exercise group	1.5	2.7	1.7	6.2	0.6

Fig. 2 – Differences between baseline and follow-up data in both groups.

LV end-diastolic and end-systolic volumes. and improvement of ejection fraction as shown in **Table 7**.

The exercise group indicated an enhancement in the distance walked during 6MWT (the distance was raised by a mean of 108 meters after 3 months), VO_{2max}, KCCQ-12 questionnaire score, ejection fraction and GLS.

Whereas the control group after three months of follow-up did not indicate any significant difference in the clinical and 6MWT data.

The patients showed lower score in KCCQ-12 at the follow-up which was statistically significant.

At follow-up, there was insignificant change in the NT pro-BNP level.

According to Table 7, the echocardiographic data revealed no significant variations in the global longitudinal strain, LV, or RV function.

Differences between baseline and follow-up data in both groups

The exercise group revealed an improvement in the distance walked during 6MWT (+108 meters), VO_2 max, KCCQ-12 questionnaire score ejection fraction and GLS that were all significant without a significant increase in the levels of NT pro BNP (**Fig. 2**).

Whereas the control group indicated a decline in the distance walked during 6MWT, VO_2 max, KCCQ-12 questionnaire score ejection fraction, GLS and NT-proBNP levels.

Discussion

About 1% to 2% of adults suffer from HF, a complicated syndrome that consists of several signs and comorbidities in addition to the cardinal symptoms.[1] HF is still a major public health issue.[2]As people age, the frequency of HF tends to rise,[3] which lowers patients' quality of life[4] and increases the financial burden on both individuals and the public health system.[5]

Even though evidence-based medication and device therapies have been successful in lowering mortality, length of stay and heart failure symptoms whereas also enhancing quality of life, many patients still suffer from dyspnea and fatigue, decreased exercise tolerance, a lower quality of life, repeated length of stay, and early mortality.[6,7]

This randomized control study was designed for estimating the short-term consequences of exercise training in those suffering from compensated chronic HF during the period from May 2022 to June 2023.

The study encompassed 107 participants who were categorized into 2 groups:

- *Control group which* encompassed participants who received the standard care of a heart failure
- *Exercise training group which* encompassed patients who received the standard heart failure care in addition to a scheduled exercise program. Patients in both groups were followed up after 3 months for changes in symptoms, laboratory, and echocardiographic data.

In accordance with our study, the exercise group significantly improved their functional ability by increasing their 6MWT distance, VO_{2max}, and quality of life by 8 points on the KCCQ-12 in comparison with the control group.

Additionally, in comparison with the control group, the exercise group experienced a significant improvement in the ejection fraction and fewer hospitalizations.

6MWT, VO_{2max}, NT-proBNP levels, heart rate, LV volumes, and ejection fraction all significantly improved when comparing baseline and follow-up data for the exercise group.

Impact of exercise training on functional capacity

In our study the distance covered during the follow-up 6MWT by the exercise group was significantly longer than that of the control group that was in concordance with **HF-ACTION** trial[19] that proved a great enhancement

in the 6-minute walk test distance (P<0.001). Similarly, **ELVD-CHF** study,[20] **Jónsdóttir S et al.**[21] and **Norman JF et al.**[22] studies showed improvement in 6MWT with exercise.

Yet, **EXERT** study[23] showed no differences between the exercise and the control groups at either 3 m (p = 0.36) or 12 m (p = 0.81) follow-up.

The exercise group's greater 6MWT distance in comparison to the control group shows that the patients' exercise capacity has improved **Spertus et al.**[24] and **Ingle et al.**[25] who revealed that a rise of 55 and 54 meters, respectively, were linked to a significant enhancement in clinical status and quality of life of individuals with HF.

Moreover, 6MWD is also known to be a well-established independent predictor of clinical outcomes in HF, with increases in such magnitude associated with favourable reductions in nonfatal cardiovascular events, heart failure hospitalisations, and cardiovascular death.[26,27]

In our study the exercise group showed an improvement in the VO_{2max} compared to the control group, the VO_{2max} was measured using heart rate equation method through the minimum and maximum heart rate during the 6MWT.

Most of the studies measure the VO_{2max} using cardiopulmonary exercise testing (CPET) but unfortunately it was not available at our institute.

Voutilainen A et al.[28] reported that 6MWT as a complement to spirometry to determine the 6MWT reliability in assessing maximum aerobic capacity comparing it with the VO_{2max} measured by the cardiopulmonary exercise test.

Our study was in concordance with **HF ACTION, CROSS-HF**[29] meta-analysis, **Edwards JJ et al.**[30] and **Gristina T et al.**[31] which showed statistically significant increase in peak VO_{2max} in the exercise group compared to control group.

This showed the effect of improved exercise capacity with exercise training in patients with heart failure; improvement in functional capacity after exercise training seems related for the most part to peripheral adaptation.[32,33]

Impact of exercise training on quality of life

Our study's follow-up quality of life assessment revealed that the exercise group outperformed the control group by 8 points on the KCCQ-12.

We decided to use KCCQ-12 that contains four subdomains: Physical limitation, Symptom frequency, Quality of life, and Social limitations.

Also, we can see that quality-of-life parameters 'feelings of being disabled and self-assessment of general well-being' were positively affected by the exercise training.

Our study was in concordance with **Belardinelli et al**.[34] who stated that only trained patients saw a significant enhancement in their quality-of-life questionnaire score after two months.

Also, **Dattilo G et al.**[35] demonstrated that anti-failure drugs as sacubitril/valsartan therapy improves significantly quality of life, physical effort resistance, BNP and NT-proBNP and NYHA functional class in patients with HFrEF.

Impact of exercise training on biomarkers

Our study's follow-up of NT-proBNP revealed insignificant differences between the two groups.

In concordance with **Ahmad T et al.,**[36] who assessed NT-proBNP at baseline and after three months later in a cohort of 928 subjects from the **HF-ACTION** trial[19] and found that at three months, the NT-proBNP levels of the exercise training and usual care groups did not change statistically significantly (p = 0.59).

Moreover, **Nilsson BB et al.**,[37] **Arad et al.**[38] and **Prescott et al.**[39] indicated no significant change in the NT-proBNP levels in both groups.

On the other hand, **Pearson MJ et al.**[40] meta-analysis explained a statistically significant enhancement in NT-proBNP (p = 0.006).

Our explanation that the biomarker measurements were made after 3 months of structured exercise training, and there is a possibility that changes in levels might have been noted after a longer exercise period.

The use of biomarkers in clinical trials are made for many reasons as an establishment of inclusion criteria, explaining therapeutic efficacy and as a target for therapy and predict adverse outcomes.

Different biomarkers may provide further insight into the downstream molecular mechanisms associated with improvements from exercise training. It could be possible that different biomarker profiles respond differently to different intervention characteristics, such as intensity, perhaps allowing further tailoring of the exercise to the individual. Furthermore, biomarkers, with their prognostic utility, may provide useful postintervention information, indicating improvements when other favourable outcomes may be absent.

The follow-up NT-proBNP in our investigation revealed insignificant difference across both groups.

Impact of exercise training on echocardiographic parameters

Comparing the control group, the exercise group–s global longitudinal strain and ejection fraction improved, according to our study's follow-up echocardiographic data. This is the first study that we are aware of those measures and evaluates changes in GLS in patients with heart failure who received exercise training.

Our study was in concordance with ***ELVD-CHF*** study,[20] **Mehani et al.,**[41] and **Hambrecht et al.**[42] which showed improvement of ejection fraction in the exercise group compared to the control group. Additionally, endurance training increased LVEF from 30 ± 8 to 35 ± 9% after 6 months of training, which is consistent with the **LEICA trial**,[43] which utilized both invasive and non-invasive assessments of LV systolic function and demonstrated that endurance training improved LVEF after 6 months of training from 30 ± 8 to 35 ± 9%.

Edward JJ et al.[30] demonstrated the effect of exercise training in both HFrEF abd HFpEF and showed that there is a significant improvement of exercise capacity and quality of life in both HFpEF and HFrEF patients. In HFpEF patients, ET significantly improved an important index of diastolic function, with significant improvements in LVEF and NT-proBNP/BNP seen in HFrEF patients only

In contrast **EXERT** study[23] and **Dubach et al.**[44] showed no variation in the ejection fraction between the exercise and control groups.

We can explain the improvement of the ejection fraction in the exercise group due to decrease in LV diameters

which causes a reduction in the left ventricular volumes and hence improvement of ejection fraction

Also exercise training leads to a partial correction of peripheral endothelial dysfunction in patients with HF.[45,46]

Given that vascular tone of peripheral arteries is component of afterload. So, it can be assumed that the reduction in cardiac size and improvement in LV performance is at least partially the result of an exercise training-induced decline in afterload.

Moreover, exercise training is known to enhance phosphorylation of the survival kinase AKT at serine 477, which is associated with an augmentation in cardiac contractility.[47,48]

Also, **Correale M et al.**[49] demonstrated the anti-remodelling effects of anti-failure medications such as beta-blockers and angiotensin receptor neprilysin inhibitor which inhibit cardiac remodelling and improve echocardiographic parameters

Aşkın L et al.[50] showed the benefits of sacubitril/valsartan on patients with low ejection fraction regarding cardiac remodelling and improvement of cardiac function.

Impact of exercise training on clinical events

In our study the exercise group had a significantly lower hospitalization rate, and a non-significant lower rate of mortality and ER visits in comparison to the control group.

This was in concordance with **ExTraMATCH,**[51] meta-analysis that revealed a significant drop in length of stay for the exercise group without a significant difference in mortality

In the HF-ACTION[20] trial, reductions in the primary endpoint of all-cause hospitalization or mortality were not statistically significant. Nonetheless, supplementary analyses that accounted for prognostic factors revealed a significant treatment impact for the primary endpoint and for reducing cardiovascular mortality and hospitalizations ($p = 0.03$).

Edwards JJ et al.,[30] **CROSS-HF,**[52] and **EXERT** [(23)] study which showed no significant difference in incidence of all-cause mortality, all-cause hospitalisation or all composite endpoints between the exercise and control groups.

Limitations

This is a single-centre study, with exercise training done only using a treadmill with no other equipment such as cycle ergometer or arm ergometer. VO_{2max} was measured utilizing the heart rate equation method not the cardiopulmonary exercise testing. They only utilized echocardiography for assessing the LV systolic function. Even so, as the gold standard magnetic resonance imaging can estimate the volumes and the ejection fraction more accurately, yet because of the extra cost and inconvenience to some patients, the test was not performed.

Conclusion

Regular exercise training in systolic heart failure patients is proven to be safe and was shown to be associated with improved in the 6MWT distance and the VO_{2max}.

Furthermore, exercise training is linked to improved GLS, ejection fraction, and quality of life in those who suffer from heart failure. Hospitalization rates were lower for patients who participated in the exercise program than for the control group, but other adverse events like mortality and emergency room visits were similar for both groups.

Conflict of interest
None.

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Ethics approval
On August 4, 2022, the Cairo University Faculty of Medicine's local ethics committee approved the study protocol, assigning it the code MD-214-2022.

Informed consent
Every participant in the study gave their informed consent.

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